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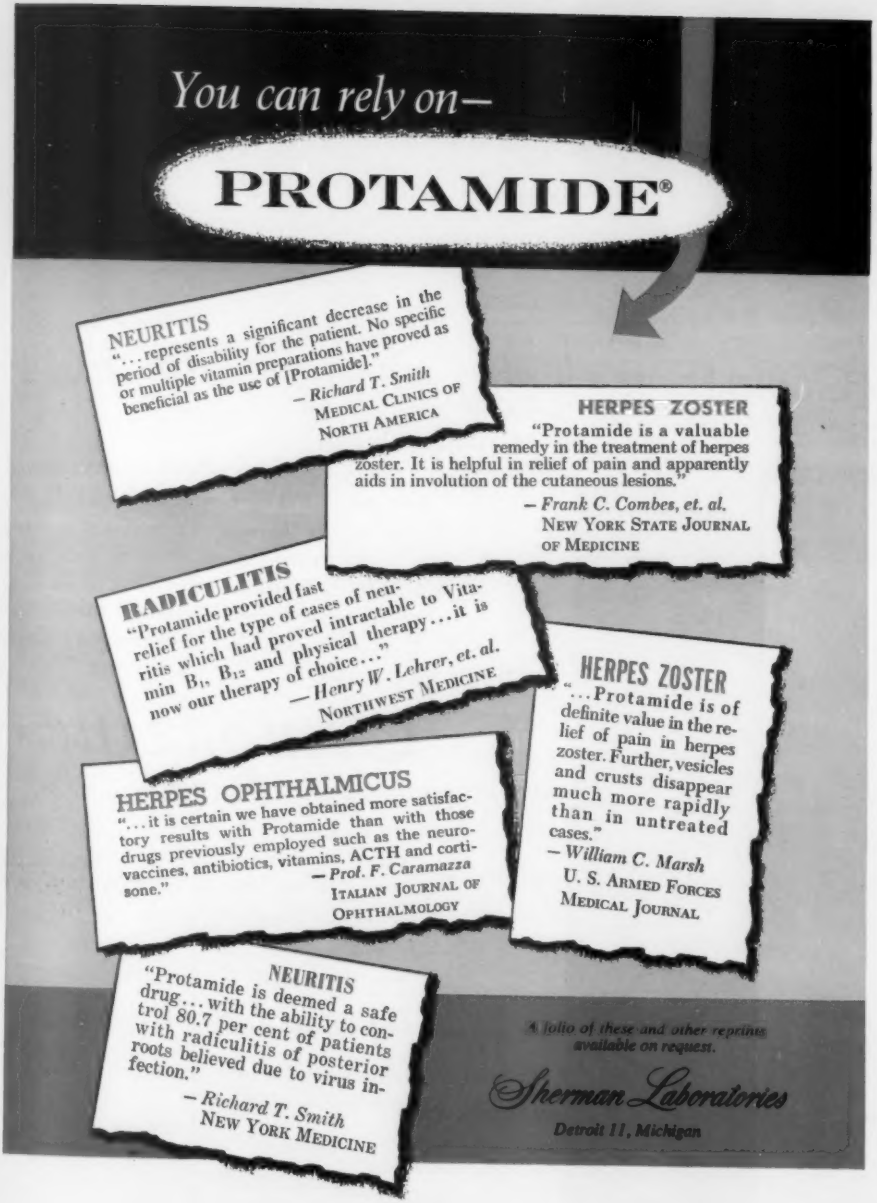
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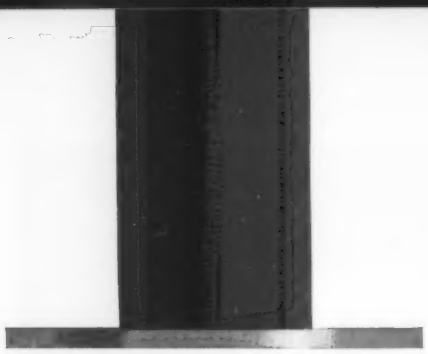

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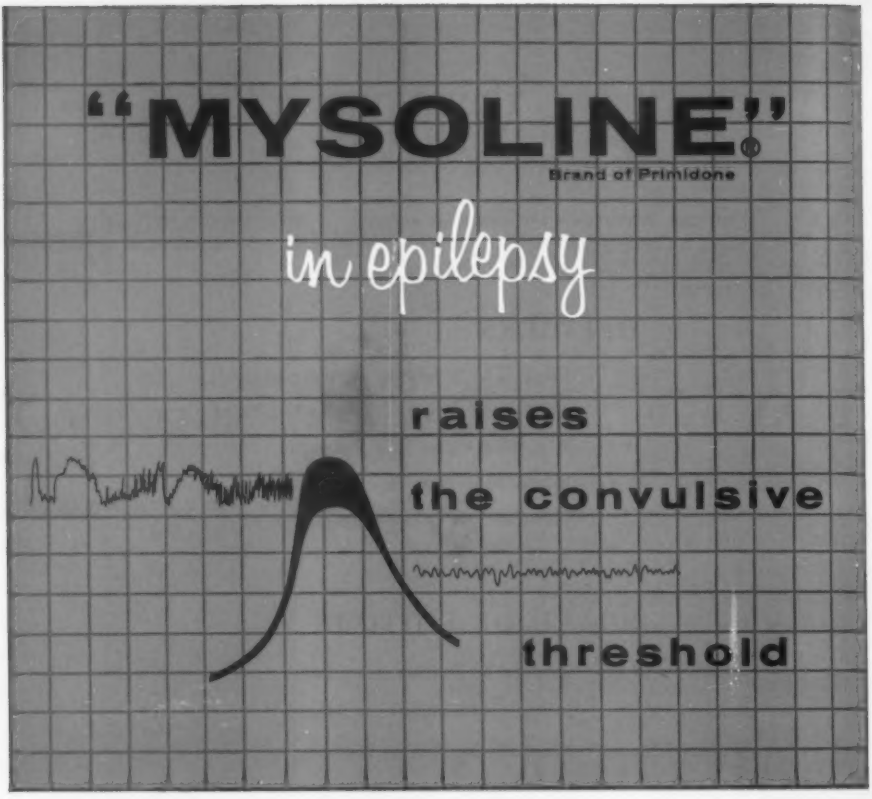

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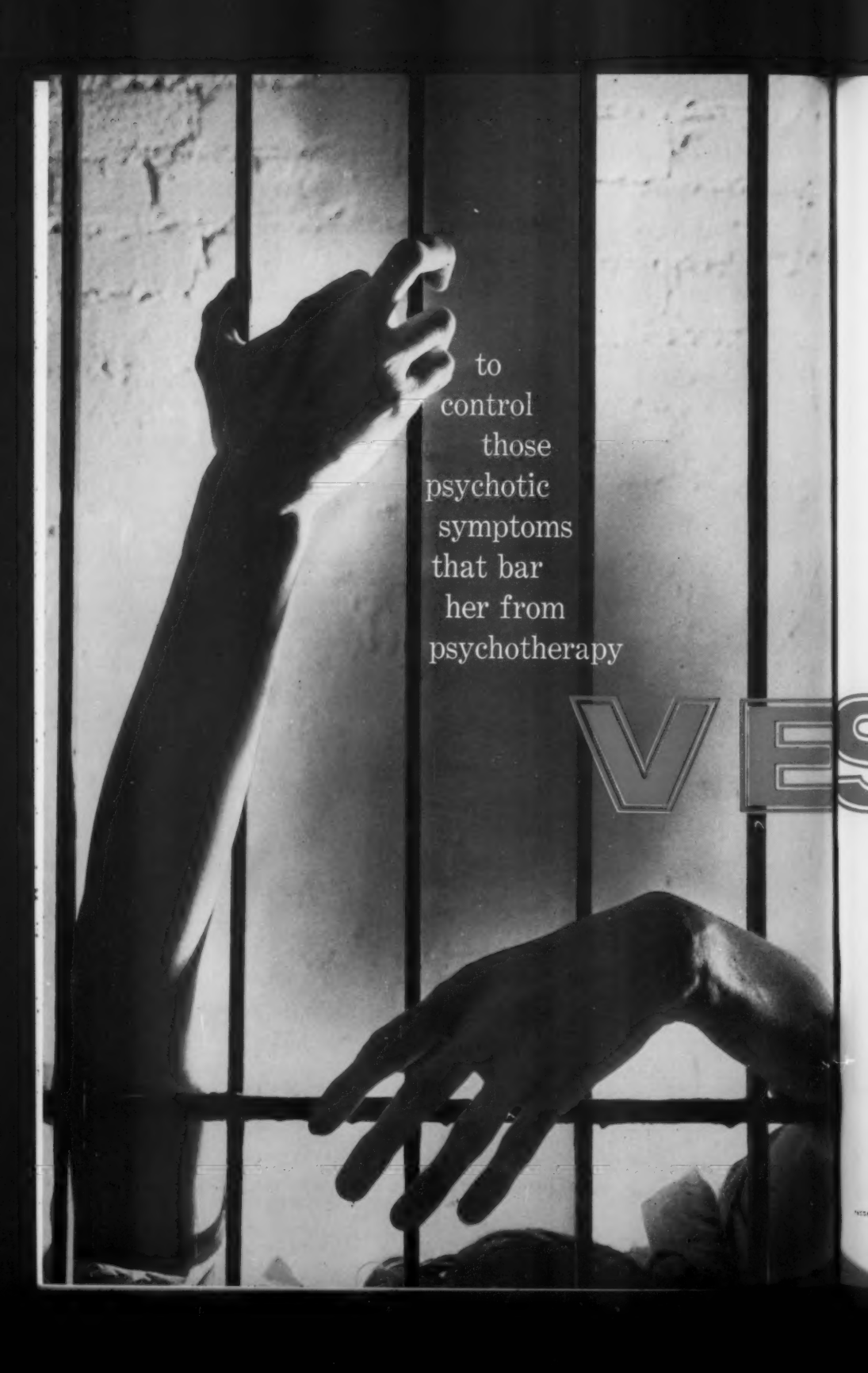
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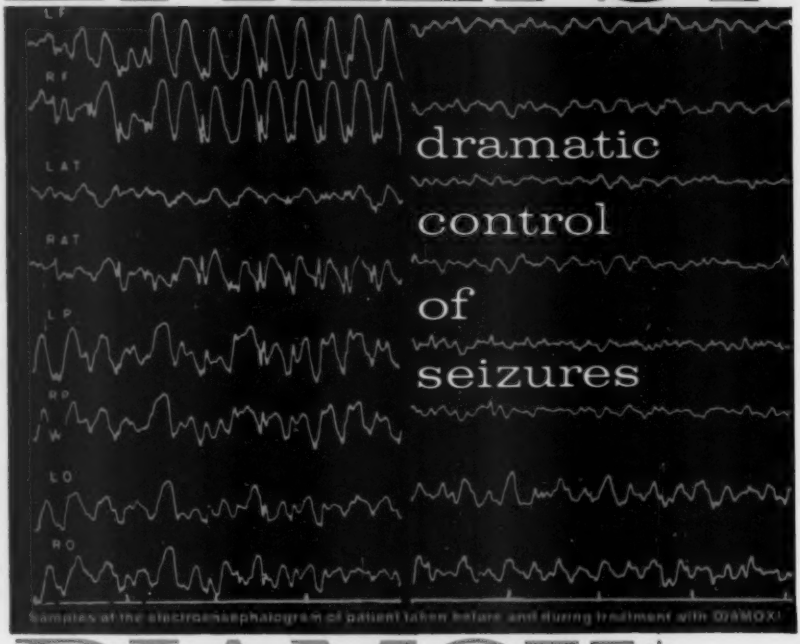

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Neurology Volume 8 • Number 9

Cluster Headaches

A. P. Friedman, M.D., and H. E. Mikropoulos, M.D.

PAROXYSMAL ATTACKS of cluster headaches have been well documented in the literature during the past ninety years under a variety of clinical entities and eponyms. The clinical picture is one of periodic, excruciating, and agonizing unilateral pain involving the eye and/or temple, associated with injection and tearing of the ipsilateral eye and stuffiness of the nose, occurring in groups or clusters. Such attacks do not fit the picture of true neuralgia or classic migraine and are frequently grouped together under the category of atypical facial neuralgia or autonomic faciocephalalgia. In recent years the best known of this group, in what is considered to be a new syndrome of vascular headache, is called histaminic cephalalgia. The purpose of this paper is to trace the history of this syndrome and discuss some observations of our own, as well as those of others, regarding its clinical picture, mechanism, and treatment. Recognition of this clinical syndrome and its treatment is of practical value, because of the severity of the pain and the need to save the patient many unnecessary procedures in diagnosis and therapy.

Many authors have described close variations of the syndrome at different times and under different names.[1,2] Mollendorff in 1867 described it as red migraine, with hemicrania, homolateral redness of face, injection of the eye, lacrimation, and dilatation of the temporal arteries. Bing in 1910 called it erythromelalgia of the head. Sluder in 1908 and 1913 characterized it as sphenopalatine neuralgia, or lower half headache. Pasteur Vallery-Radot with Blamoutier and others, in 1925 and in subsequent years, published reports of such cases under the title "syndrome of hemicephalic vasodilatation of sympathetic origin." Harris in 1926 and 1936 called it ciliary (migrainous) neuralgia. Later, in 1932, Vail used the term vidian neuralgia. Brickner and Riley in 1935 preferred to call it autonomic faciocephalalgia.

Horton, McLean, and Craig[3] in 1939 spoke about a new syndrome which they originally named erythromelalgia of the head but changed to histamine cephalalgia in 1941.[4] Gardner and co-workers[5] in 1947 described it as petrosal neuralgia. Symonds[6] in 1956, in agreement with other authors,[7,8] thought of it as a migraine variant. Among the others who reported similar cases in the literature are: Dandy (1931),[1] Taptes (1948),[1] Lenormand (1948),[1] Kunkle and associates (1952),[7] and White and Sweet (1956).[2]

Various other names have also been used for description of the above syndrome, such as atypical facial neuralgia, Sluder's headache, Horton's headache, and so on.

From the headache unit, Montefiore Hospital, New York City.

Read at the tenth annual meeting of the American Academy of Neurology, Philadelphia, April 25, 1958.

PATHOGENESIS

Almost as many theories exist as authors who described the syndrome. Most of the theories seem to agree that we are dealing with periodic attacks of local dilatation of extracranial vessels in areas mainly supplied by the branches of the external carotid arteries. However, this alone does not explain the secretory phenomena and other associated manifestations, such as gastrointestinal symptoms (28 per cent in present series), scotomata, generalized manifestations from the autonomic nervous system, and the photophobia that we have found in 22 of our cases. In support of the hypothesis of vasodilatation are the distended temporal artery in some of the cases, the injection or even bloodshot appearance of the eye, the congestion of the nose, the local increase of the skin temperature, the occasional relief upon compression of the temporal or carotid artery, and the usual good response to vasoconstrictive agents, as all of the above were found to be present in some of the cases.

On the other hand, controversial results were obtained when attempts were made to relieve the headache by intrathecal injection of normal saline, which was given to increase the intracranial pressure.[7] Occasional relief of an attack by application of ice on the forehead or by keeping the hands in cold water and accentuation of the symptoms by blowing hot air on the face, inhalation of amyl nitrite,[1] and by administration of nitroglycerine have all been interpreted as evidences in support of the vasodilatation theory. Also in favor of the theory that dilatation of extracranial vessels is responsible is the fact that, since epinephrine does not constrict the intracranial vessels, the relief it gives during such attacks must be due to the vasoconstriction of dilated extracranial vessels. Nevertheless, for strictly anatomic reasons, it is evident that some terminal branches of the internal carotid artery in the areas of the nose and eye are also dilated.

As for the cause of vasodilatation, many authors have implicated abnormal efferent nerve impulses originating at the ganglia or nerves that supply the area, while others have suggested the release of some chemical substance locally and periodically. Others finally proposed a combination of such factors. Authors who support the former mechanism spoke of neuralgia and named the syndrome according to the suggested origin of the neuralgia; they also tried to establish some kind of treatment. Sluder named it neuralgia of the sphenopalatine ganglion and spoke of the remarkable effects of cocainization of the ganglion. Vail, implicating the vidian nerve, preferred the term vidian neuralgia. Gardner and his associates[5] called it greater superficial petrosal neuralgia, supporting the view that periodic discharges of parasympathetic impulses of the greater superficial petrosal branch of the seventh nerve should cause unilateral lacrimation, swelling, secretion of the nasal mucosa, and unilateral head pain. They tried section of the nerve, but finally commented that the procedure is not justified, since one-half of the patients did not obtain enough relief.

White and Sweet[2] also tried petrosal neurectomy and concluded that their data were too fragmentary to permit any final decision concerning the value of neurectomy. They suggested that good results are related to interruption of afferent pathways of pain rather than of efferent fibers mediating vasodilation.

Kunkle and his associates[7] suggested that there probably is an increased susceptibility of the carotid artery of those patients to diverse vasodilating agents and said that this might be the reason for induced headache by histamine or alcohol.

Pasteur Vallery-Radot and his associates[1] felt that some kind of involvement of the sympathetic system is present. They seem to agree with Barbizet, who spoke of acute reflex dilatation of the arterioles and capillaries in the territory of one or more branches of the external carotid artery, with perception essentially with the trigeminal and perivascular plexuses and with a response through the elements of the sympathetic and parasympathetic of those plexuses. They finally conduded that a local cause, ocular, nasal, or dental, is found in most of the cases. As for the problem of existing local foci, most other authors did not find them to exist in an appreciable percentage. All of Symonds'[6] patients were negative. Only six per cent of our cases had some kind of sinusitis or nose abnormality.

On the theory that some kind of vasodilating factor is released locally, Horton[3] expressed the belief that this factor is histamine, with

which he has been able to provoke attacks and treat the syndrome by desensitization. Wolff[8] stated that the mechanism of vasodilatation during an attack is unknown, and that "it would appear that an agent liberated locally causes a circumscribed vasodilatation reaction." He also suggested the possibility that both histamine and acetylcholine, or other vasodilating agents as well, might act. He concluded that, although histamine is a convenient agent for production of experimental headache, and although it is possible to precipitate headache more readily in patients with migraine or histamine cephalalgia, this does not justify the inference that histamine is the responsible vasodilator agent. He also pointed out that the headache following a single intravenous injection of histamine lasts from two to 12 minutes and produces a dilatation of the intracranial arteries and especially of the large arteries at the base of the brain, including the internal carotid, vertebral, and basilar arteries and their main branches. Horton, on the other hand, did not find the generalized headache induced immediately following the administration of histamine, which he called histamine headache, of diagnostic value. He emphasized the importance of a delayed unilateral headache, which he called histamine cephalalgia, which appears in about 30 to 50 minutes and after a free interval following the original generalized headache. Horton[10] has some well documented cases to substantiate his theory; however, most authors, including ourselves, do not agree on the specificity, existence, or value of the test. Pasteur Vallery-Radot[1] commented, "We do not conceive at all these two cephalalgias of different character on the same subject after the administration of histamine. Also we think that the theory of histamine is very doubtful." The delayed reaction to histamine was only an occasional part of our experience, and we cannot differentiate these patients by their history, examination, or clinical response to treatment from the rest of the patients we have studied. Gardner[5] reported that attacks were not induced by histamine in his 13 cases.

Wolff[8] was able to reproduce a right-sided headache attack with minimal intravenous injection of histamine in a patient with migraine. Von Storch[11] gave histamine intravenously and found that patients with migraine were most susceptible. Those with chronic headache were less susceptible and those without, the least susceptible. Among the migraine subjects over 90 per cent of the experimentally induced headaches were similar to the migraine headache.

Friedman and Brenner[9] reported that they reproduced unilateral posttraumatic headache with histamine intravenously and suggested that the mechanism of production of posttraumatic headache is the same one as for the histamine headache.

Horton[10] recognized that the reproduction of an attack and its subsequent abortion was not always possible. He also added that 1/50 grain of glycerin trinitrate can frequently precipitate an attack of histamine cephalalgia, but he did not consider it a satisfactory provocative test. He could not reproduce the headache with nicotinic acid. He also suggested that other biologic agents such as acetylcholine may be liberated in the pain area, which might account for the secretory phenomena of the lacrimal glands and the mucous membranes of the nasal cavity. It has been a long disputed point that a simple vasodilation caused by any factor can produce secretory phenomena as well.

Horton[10] mentioned that during an attack the acidity of the gastric contents increases abnormally to a level comparable to the one induced by histamine injection, but Kunkle,[7] commenting on this, felt that this may simply be a result of a nonspecific stress.

Trauma has also been suggested as a cause of cluster headaches. Hunter and Mayfield[2] have reported eight cases where the upper cervical nerves were injured following a whiplash injury to the neck which produced, in addition to discomfort in the suboccipital region, attacks closely resembling those of the syndrome under discussion. Several interesting hypotheses have been suggested for the explanation of spread of pain from the neck to the forehead and face via the spinal fifth or sympathetic fibers.

The always appealing theory of some kind of allergy due to foods or inhaled allergens as the cause of the syndrome has been advocated by different authors. Nevertheless, the percentage of patients who show other evidence of allergy by history or tests is small in all

series; skin tests alone do not provide satisfactory evidence of food allergy in headaches, and both allergy and headache may coexist independently in the same person. The incidence of allergy is not greater in this group than in the general population.

On the other hand, treatment with antihistamine drugs and dietary or other antiallergic precautions has always given poor results and, when successful, is of transitory nature.

PSYCHOLOGIC FACTORS

The psychologic backgrounds of our patients were not studied in detail, except in a few patients who were under psychotherapy. Although it was not possible in many of these patients to verify that the primary etiology is psychogenic, the importance of psychologic factors in their headache problem cannot be minimized.

The personality pattern most commonly observed was that of an adult who was ambitious, efficient, and overconscientious, strove for perfection, and had a strong tendency toward compulsive behavior, in other words, a constitutional predisposition to sustained emotional states. They often had positions of responsibility but were insecure and often had a lack of self-confidence in their ability. The most frequent conflicts observed were of a hostile and aggressive nature. A similar personality type is observed in patients who have classical migraine, hypertension, ulcers, or no illness. It was unusual to find that the initial painful attack occurred with a known disturbing emotional experience.

It was particularly interesting that many of these patients could not recognize that they were under greater stress or more emotionally upset or fatigued prior to an attack than in the preceding months or years. Furthermore, during their attacks they continued to work, in spite of loss of sleep, pain, and increased stress, which does not usually change the duration of each bout of cluster headache. They occur and continue whether the patient is at work or on vacation, on land, ocean, or desert, in warm or cold weather, or in dry or wet climates.

It seems apparent that patients with vascular headaches of the migraine type react physiologically to emotional tension by delayed response, which is not true of other forms of bodily reaction to emotional tension, for example, blood pressure, cardiac rate, gastric secretion, and motility of colon. The major cranial arteries seem to be more stable and follow a different pattern of reaction.

It is still undecided whether the resultant tensions which develop from personality reactions to life can explain these attacks. However, it is our belief that they are closely related. It is of interest that, of three patients who have been under psychotherapy, no attacks have occurred in two, for a period of two years, and in one, in the past year.

DESCRIPTION OF THE SYNDROME

General considerations. The age, sex, familial history of headaches, race, occupation, and season are summarized in table 1. It should be added that the average age was found to be 28 in the present series; over 40 in Horton's series,[10] although it is not stated if this is the age of onset of the syndrome; and 27 in Symonds' series. The duration of the illness in the present series was two to 37 years (average 12.8 years). The 20 per cent found to have a family history of headaches is lower than the percentage found in our studies of patients with migraine (65 per cent) or of patients with tension headache (40 per cent).

Alcohol was a provoking factor in 50 per cent, emotional stress in 54 per cent, and fatigue, bright light, and weather change in smaller numbers. Horton[10] found that histamine provoked an attack in 69 per cent, alcohol in 45 per cent, ACTH occasionally, and nitroglycerine frequently; he also emphasized the significant role of nervous tension. Symonds found that alcohol and seasonal changes were provoking factors in a small number of patients, but he did not find any evidence of psychologic factors.

The past medical history was as follows in the present series: Some type of head injury, with or without loss of consciousness, 16 per cent; allergy, 12 per cent; sinusitis or nose abnormalities, 6 per cent; psychotic disorders, 4 per cent. There were also sporadic cases of coronary, polio (two), Bell's palsy, birth injury, inactive syphilis (two), psoriasis (one), and eczema (one).

TABLE 1
GENERAL CONSIDERATIONS

Age at Onset:	*Our Series* 11 to 44 years	*Horton* 21 to 76 years	*Kunkle* 17 to 40 years	*Symonds* 14 to 43 years
Sex: male	4.5	6.6	4	4.6
female	1	1	1	1
Headaches in family	20%	Some	33%	33%
Provoking factors	Alcohol; emotion	Histamine; alcohol	Alcohol	Alcohol
Race	Mostly Caucasian			
Occupation	Mostly executive or professional level			
Season	Predominantly fall and spring.			

In Kunkle's[7] series, evidence of tension was found in over 50 per cent. In Symonds' series of 17 patients, three had a history of hay fever and two of head injury.

Physical findings. In our series, the physical findings were unremarkable, except for one instance of unequal knee-jerks found in a patient with an old history of syphilis, one case of atrophy of one hand following birth injury, one patient with sinusitis, two patients with tenderness of the neck muscles, one with right ptosis, one with Horner's syndrome, and one with nystagmus.

Laboratory findings. In a small group of patients studied, preliminary results indicate an increase of lysine excretion during headaches, as compared with the headache-free period. Derangement in lysine metabolism is suggested by qualitative comparison of dimensional electrophoresis patterns. There was a rise of urinary excretion of 17-ketosteroids above normal level during the headache period, in contrast to patients with migraine in whom a fall occurred in 17-ketosteroid excretion. During the headache-free period, the 17-ketosteroid excretion was at normal levels in these patients. However, results of this study as yet do not allow definitive conclusion, although this fragmentary evidence supports the tentative hypothesis of a biochemical change occurring during these attacks. No evidence of change in glucose tolerance was observed prior to or during the period of attacks. Normal electroencephalograms were obtained in our patients, and no evidence of electrical anomalies were noted during the symptom-free period or period of attack. Routine urinalyses, blood counts, and roentgenograms of the skull were within normal limits. Special examinations such as basal metabolic rate and visual fields studies were all within normal limits.

Temporal factors of the bouts and paroxysms. The averages of these factors are given in table 2. It should be added that the duration of the bouts in the present series was found to be from one to 16 weeks. In 50 per cent of the patients it was six to eight weeks. The duration was variable in each individual patient as well, and the minimum

TABLE 2
AVERAGES OF TEMPORAL FACTORS

	Our Series	*Horton*	*Kunkle*	*Symonds*
Duration of bouts	4 to 10 wk.	—	Days to wk.	1 to 10 wk.
Interval between bouts	7 to 18 mo.	—	2 to 24 mo.	2 mo. to 10 yr.
No. of paroxysms per 24 hr.	1 to 3	1 to 3	1 to 5	1 to 8
Duration of paroxysms	½ to 2 hr.	Less than 1 hr.	Less than ½ hr.	¼ to 2 hr.
Paroxysms more frequent at night	50%	Over 50%	—	Over 50%

TABLE 3
CHARACTERISTICS OF ATTACK

	Our	*Horton*	*Kunkle*	*Symonds*
Prodromata	Very rare	None	Very rare	None
Main characteristics of pain	Stabbing; throbbing	Excruciating; burning	Intense	Sharp; stabbing or throbbing
Main associated manifestations	Nasal congestion, lacrimation, ocular injection	Lacrimation, ocular injection, nasal congestion	Nasal congestion, ocular injection, lacrimation	Ocular injection, lacrimation, nasal congestion
Commonest location of pain	Orbital; frontotemporal	Orbital; temporal	Orbital	Supraorbital; orbital
Laterality	Right more than left	Right equal to left	Right more than left	—

was found to be approximately one week and the maximum one month. Horton,[10] without giving figures, stated that the attacks tend to occur in series and may occur repeatedly, very often on a seasonal basis.

The intervals between bouts were quite variable in the present series, ranging from a minimum of three months to a maximum of five years. The given average is based on 66 per cent of the patients. Fifty-four per cent of the patients had at least one attack every year. For each individual patient, the interval between the bouts was found to be fairly regular in about 40 per cent, while in another 44 per cent variations between one-half and two years were found.

While 90 per cent of our patients had one to three attacks in 24 hours, the minimum number of attacks was two per week and the maximum four per day. The number of paroxysms in 24 hours for each individual patient was found, in 60 per cent of our patients, to be variable in each individual patient, usually plus or minus one the usual number of attacks for that individual. The occurrence of paroxysms at night only was found in 12 per cent, while patients who reported attacks more frequently at night constituted 36 per cent of the total group.

The duration of paroxysms was found to be one-half to two hours in 86 per cent of our cases. A minimum of some minutes and a maximum of six hours was found in exceptional cases. For each individual patient the duration of the paroxysm was usually variable, from one-half to one hour plus or minus his usual timing.

Characteristics of the attack. These are shown in table 3. Prodromata such as numbness in the area of the pain, slight ache above the nose, nasal congestion, and sweating on face or body were considered very rare in our series (less than 10 per cent). Kunkle[7] reported exactly the same kind of prodromata in rare instances.

The headache pain was classified as stabbing, piercing, or knifelike in 56 per cent, throbbing or pounding in 38 per cent, and unqualified sharp in 30 per cent. Only one patient complained of burning headache, and three had a dull pain.

Most authors found a sudden onset and an abrupt end. According to Symonds,[6] the attack begins with an intense pain which comes to a plateau in ten to 20 minutes, lasts another 20 minutes, and then diminishes rapidly. In the present series, termination of the attack was rapid in most patients.

The associated manifestations in our series were: congestion of the eye in 50 per cent; lacrimation in 80 per cent; stuffiness of the nose in 88 per cent; rhinorrhea in 10 per cent; gastrointestinal symptoms, such as nausea or vomiting or severe anorexia, in 28 per cent; symptoms from the autonomic nervous system, such as sweating, chilly feelings, and the like, in 20 per cent; photophobia in 22 per cent; and different psychologic reactions in 14 per cent; there was one case of periorbital edema. In our experience, evidences of vasodilatation were manifested in many patients by the triad of dilation of the temporal vessels, injection of the eye, and stuffiness of the nose. Pulse wave studies in our patients would tend to substan-

TABLE 4
DIFFERENTIAL DIAGNOSIS

	Cluster Headache	*Migraine*
Family history	Less than 20%	Over 65%
Average age of onset	28 years	Less than 20 years
Bouts	Yes	No
Paroxysms	More than one per day	Less than one a week
Duration of paroxysms	Shorter	Longer
Prodromata	Very rare	75%
Distribution	Mostly orbital	Mostly supraorbital or cranial
Visual disorders and gastrointestinal symptoms	Rare	Common
Lacrimation, nasal congestion	Common	Very rare

No differentiation can be based upon quality of pain or response to ergotamine.

tiate the concept that vasodilatation with increased amplitude of pulsation occurred during an attack.

Different authors have pointed out that the eye may appear bloodshot, the temporal vessels may be swollen, the temperature of the face may be increased, and rhinorrhea may be present instead of stuffiness of the nose. Horton[4] considered Horner's syndrome not uncommon and denied the presence of gastrointestinal symptoms in any of his cases. Kunkle[7] and Symonds[6] reported nausea and vomiting in some of their cases.

Location of the pain. In 64 per cent of the present series the pain was orbital; in 40 per cent supraorbital; 22 per cent frontal; 28 per cent temporal or parietal; and 4 per cent occipital or in the neck. In 12 per cent we have found hemifacial pain, and in 8 per cent the pain was hemicranic in type. In one case the pain started from the right and spread to the left. In our experience, no bilateral or alternating headaches occurred.

As to laterality, Horton[10] stated that the pain is mostly unilateral; Symonds[6] found it strictly unilateral in a single bout but one of his patients, who for 16 years had right-sided attacks, started to have left-sided ones. Kunkle found alternating sides of pain in one-seventh of his patients, bilateral involvement in one.

DIFFERENTIAL DIAGNOSIS

Regardless of the fact that some authors think of the syndrome as an entirely distinct entity, while others recognize it as a distinct variety of migraine, the chief differential diagnosis is to be made from classic migraine. The main criteria are given in table 4. It should be added that migraine manifests itself in more widespread disorganization of bodily function.[11]

The initial vasoconstriction of certain intracranial branches of the internal carotid artery that produces visual and possibly other preheadache phenomena common in migraine should be considered as absent in cluster headache.

Horton agreed that there are some cases where the boundaries of migraine and the so-called histamine cephalalgia are not distinct, and he presented a case that he diagnosed as 70 per cent migraine and 30 per cent histamine cephalalgia.[12] Kunkle concluded that half of the features of the cluster headache may be found in some cases of migraine and he considered it as a migraine variant.

It is of interest to note that, unlike most of our migraine headache patients who like to remain quiet during an attack of headache, patients with cluster headache move around actively during the painful phase of the attack.

No serious diagnostic problems can arise in making the differential diagnosis of cluster headaches from typical forms of cranial nerve neuralgias, such as trigeminal, facial neuralgia (geniculate, herpes zoster), glossopharyngeal, vagus nerve neuralgia (superior laryngeal and aural), and occipital and cervical neuralgias.

TABLE 5
DIFFERENTIATION OF TYPICAL AND ATYPICAL NEURALGIA

	Typical	*Atypical*
Distribution of pain	Limited in the field of one of the cranial nerves	Does not follow nerve distribution
Character of pain	Paroxysmal, sharp, localized	Diffuse, deep-seated, poorly localized; described as pulling, gripping, etc.
Duration of pain	Seconds to minutes	Hours or days
Autonomic nervous system signs	None	Lacrimation, flushing, nasal congestion, other symptoms
Precipitation by external stimuli	Yes	No
Trigger zone	Present	Absent
Age	Older age group	Younger age group
PHARMACOLOGY		
Vasoconstrictor	No relief	Frequent relief
Vasodilator	Inadequate relief	No relief
Narcotics	Inadequate relief	Frequent relief
Relief by surgical or chemical interruption of cranial nerve	Relief	No relief
Personality	Neurotic traits not prominent	Neurotic traits prominent

In these typical neuralgias, pain is limited to the field of one cranial nerve and lasts usually from seconds to minutes; there are no autonomic nervous system signs; pain can usually be precipitated by external stimuli; a trigger zone exists; the vasoconstricting medications do not help, while surgical or chemical interruption of the nerve is usually successful.

On the other hand, the following criteria may help in making a differential diagnosis of cluster headaches from certain atypical facial neuralgias. The latter are characterized by their deep-seated and poorly localized pain, their short or very prolonged duration, and the fact that in many instances pain is initially periodic but may become continuous. The majority of such patients are female, more clearly suffering from psychoneurotic conversions or compulsive reactions, and there is frequently a history of initial pain occurring at the time of a significant event in the emotional life of the patient. Table 5 may be of further help in differentiating the above syndromes.

Horton,[12] making the differential diagnosis of unilateral recurrent erosion of the cornea, pointed out the pain in the orbit and the erosion of the cornea which are present in that syndrome.

No differential diagnostic problems exist between the syndrome and tension headaches, except in those patients who have occipital and scalp headache associated with pain in the face and forehead. It is assumed that the central spread of excitatory effect of noxious stimulation of the soft tissues of the neck is responsible for the facial and forehead pain. This spread of pain is carried by the upper cervical nerves either via the spinal fifth or autonomic nervous system. The history and clinical course of tension headaches help to differentiate the two conditions.

Cephalalgias secondary to injury of upper cervical nerve can present a picture which resembles cluster headache. Hyperextension of the neck or rotation of the occiput to the painful side usually produces the pain, and procainization of the second cervical root usually stops it. The history of trauma and clinical course should clearly differentiate these two conditions.

Cluster headaches must also be differentiated from cephalalgias secondary to a variety

of other causes. These include pain of dental origin; tumors of the mandible; ocular disorders; disturbances of the nasal and paranasal structures; tumors of the nasopharynx; tumors of the cranial nerves, mainly the eighth and fifth, and cerebellopontine angle; aneurysm and anomalies of blood vessels; temporal arteritis; postherpetic neuralgia; sarcoidosis; and posttraumatic headache. Differentiation of the above conditions can be based upon the history, clinical course, and physical findings.

TREATMENT

Treatment should be considered from two viewpoints, prophylactic and symptomatic.

Horton proposed the use of repeated subcutaneous injections of histamine in increasing doses in order to desensitize the patients to the histamine that is considered the etiologic factor. In his original publication[3] Horton reported very favorable results temporarily or for longer periods of time, but he did not give statistical follow-up results. In the same article he reported that histamine given to other patients as well was found to be temporarily effective in most cases. In 1952[10] Horton reported that the adequate dose is determined only by the patient's response, and he again pointed out that, if the symptoms are aggravated or seem to be precipitated by the injection, the patient may be undergoing sensitization rather than desensitization. He recommended a two- to three-week series of twice daily self-administered subcutaneous injections of histamine and once daily thereafter for an indefinite period of time. He added that some patients find it necessary to use two or three injections per day; he felt there was no harm in continuing this, even for a lifetime. Ninety-five per cent of his patients responded well, and their attacks ceased in 10 to 20 days. The desensitization is especially difficult, according to him, if the patient has had previous histamine treatment. In general, he has found a 92 per cent good response and 36 per cent recurrences within one year. Recently Horton also advocated the use of whole cortical extract, ACTH, or cortisone, 100 mg. intravenously daily, three or four days or longer before beginning desensitization. In 1956[13] he concluded that histamine treatment is neither simple nor commonplace but fraught with pitfalls.

Pasteur Vallery-Radot[1] reported that the histamine treatment is deceiving and that symptoms were aggravated by it in four cases. He also recommended elimination of local irritative foci.

Symonds[6] expressed serious doubt as to the validity of histamine treatment. Kunkle and his associates[7] also doubted its validity and felt that the histamine drugs are quite ineffective. Histamine desensitization was tried by the authors. Thirty-five patients in our series received histamine desensitization either from us or the referring physician. One to five series were given, followed by continuation of administration of histamine in maintenance doses. No beneficial results were observed in 18 cases (51 per cent). Doubtful results or reports of relative success with an original series followed by failure in subsequent ones were found in eight cases (23 per cent). In three cases (9 per cent) the patients became worse with histamine treatment. In five patients (15 per cent) good results were reported, but in all cases the results were temporary. Here again, the interpretation is difficult because of subsequent remissions, spontaneous remissions of the bouts, and the intervals between them. Because of the long duration of each series, the end of which may coincide with the termination of the bout itself, it is very difficult to be sure of the effect, even in that 15 per cent.

Antihistamines were tried in one-half of our patients, with definitely negative results in 50 per cent of them. Slight improvement or doubtful results were found in the rest. Horton[4] and Kunkle considered antihistamines of no value. Pasteur Vallery-Radot thought that antihistamines may be helpful only because of their action to decrease the permeability of the capillaries.

Symonds and Horton[10] advocated also the use of injections of ergotamine or the administration of suppositories of 2 mg. of ergotamine plus 100 mg. of caffeine at bedtime as measures to prevent nocturnal attacks. In our series of 35 patients, ergotamine preparations were administered by mouth, in suppositories, or by different kinds of injections, under all the known names, such as ergotamine tartrate, dihydroergotamine (D.H.E. 45), and Cafergot, and these proved to be effective to a

TABLE 6
ERGOTAMINE PREPARATIONS USED IN ACUTE ATTACK

Medication	*Amount*	*Form*	*Dosage*	*Action*	*Side Effects*	*Contra-indications*
Ergotamine tartrate (Gynergen)	{ 0.25 mg. 0.5 mg.	amp.	0.25 to 0.5 mg.	Vasoconstriction	Nausea, vomiting, numbness and tingling of hands and feet, muscle pains in thighs and neck, abdominal pain, prostration	Septic infectious states, vascular diseases, coronary sclerosis, history of angina, pregnancy, hypertension, impaired renal or hepatic function
Ergotamine tartrate (Gynergen)	1 mg.	tab.	2 to 6 tabs.	Same	Same as above	Same
Ergotamine tartrate Caffeine (Cafergot)	1 mg. 100 mg.	tab.	2 to 6 tabs.	Same	but less pronounced	
Ergotamine tartrate Caffeine (Cafergot)	2 mg. 100 mg.	suppos.	1 to 3 suppos.	Same		
Dihydroergotamine (D.H.E. 45)	1 mg.	amp.	1 to 2 mg.	Less vasoconstricting than ergotamine tartrate		

greater or lesser extent in 85 per cent (30 patients). Table 6 shows the main ergotamine preparations, their dosages, side effects, and contraindications. These medications have been used symptomatically during periods of bouts. Due to the transitory nature of the attacks, the best results were obtained when ergotamine or dihydroergotamine was used parenterally. However, this method had certain handicaps, including the difficulties encountered in administering a drug by injection and the fact that many patients are unable to give themselves an injection. Use of Cafergot in suppositories proved to be more effective than when used by mouth and more rapid in its action.

All authors agree that the administration of ergotamine preparations should be early enough during an attack in order to be of value. Others have also obtained good results with ergotamine preparations.

Horton[10] recommended breathing 100 per cent oxygen with a mask in combination with 1 cc. of D.H.E. 45 intravenously at the beginning of an attack. Several of our patients have responded quite favorably to oxygen at times, although in general this has not proved to be as effective as the vasoconstricting agents such as ergotamine.

The use of epinephrine given subcutaneously or intravenously is effective, according to most authors, if given early during an attack. Compression of the external carotid or its branches, especially the temporal artery, has been reported of some value during an attack in certain cases.

The use of cortisone alone by the authors and by Horton[10] was of no value. Tranquilizers, Belladenal and Bellergal, were not helpful in our experience. Demerol and codeine were used in 11 patients, with good results in 50 per cent of them. Mild analgesics or sedatives, such as aspirin, Empirin, and Fiorinal, were tried in one-half of our patients, with good or moderate results in only 25 per cent. Psychotherapy, used in a small number of patients, proved to be of some value.

Wolff,[8] commenting on treatment, stated that the attacks are modified in intensity and severity by suggestive chemotherapy, other nonspecific medical attention, resolution of personal problems, emotional support, rest, and reassurance.

Surgical approaches to the problem have been described in great variety. Ninety per cent of Horton's patients had already undergone some surgical treatment unsuccessfully before they visited his clinic.[13] Greater superficial petrosal section was cited by Gardner.[5] White and Sweet,[16] also without success, tried neurectomies on the external greater or lesser superficial petrosal nerves.

Cocainization of the spinal ganglia, supraorbital blocks, ligation of the veins in the areas under the chin, ligation of the temporal artery, repeated sphenopalatine ganglion blocks, removal of the sphenopalatine ganglion, and avulsion of the occipital nerve, all done in a number of patients before they were under our observation, proved to be of no value whatever. The same lack of permanent success is reported by other authors.

DISCUSSION

We believe that we are dealing with a specific clinical entity which is probably related to the migraine type of vascular headaches.

There has been much confusion in the literature regarding this syndrome, because cases with many similar symptoms and signs (and with some dissimilarities of lesser interest) have been discussed under various terms.

The syndrome is not as uncommon as one might be led to believe from the literature. The present series represents a sampling of 50 consecutive cases from a much greater number studied in the past ten years.

The pathogenesis of the syndrome appears to be primarily vascular, consisting of vasodilatation of branches of the external carotid artery and, to a lesser extent, of portions of the intracranial circulation.

The definite cause of the vasodilatation is still unknown but is probably a combination of neural and chemical factors. Some preliminary indications of biochemical changes have been observed. Psychogenic factors also seem to be of significance.

Although we feel that the syndrome belongs to the group of migraine type of vascular headaches, we consider it different from classic migraine and feel that further studies are worthwhile. The main reason for this is that, because of its particular history, nature, and clinical symptomatology, the syndrome has been confused with both the typical and the atypical neuralgias of the head. The result has been an improper diagnosis and application of unsuccessful or dangerous therapeutic measures.

There is no adequate prophylactic treatment at this time, other than reduction of stress factors. Ergotamine is effective symptomatically.

SUMMARY

The history and pathogenesis of the syndrome of cluster headaches in 50 patients has been reviewed critically.

The average age at onset is 28; the male sex was affected in the ratio of 4.5:1; and a family history was found in 20 per cent.

In average figures, the duration of bouts was four to ten weeks, the interval between them was seven to 18 months, the number of paroxysms per day was one to three, and the duration of paroxysms was one-half to two hours. Prodromata were very rare; the pain was mostly stabbing or throbbing; the predominant associated manifestations were nasal congestion, lacrimation, and ocular injection; the most common location of the pain was orbital or frontotemporal.

The differential diagnosis of the syndrome concerns its separation from classic migraine, typical and atypical neuralgias of the head, tension headaches, and other less common conditions. Some hypotheses regarding pathogenesis have been suggested.

The various therapeutic approaches have been presented and the symptomatic value of ergotamine preparations emphasized.

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The prognosis of some brain stem vascular syndromes

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WITH RECENT INTEREST in anticoagulant therapy in the treatment of vascular thrombosis of the brain has come an awareness of our lack of knowledge of the natural course of this difficulty. Attention has been focused on insufficiency and thrombosis of either the basilar or carotid arteries, and treatment of these syndromes with anticoagulants in selected patients has become common. Therapeutic results have been somewhat uncertain because the natural untreated course of the disease has been unknown.[1–11]

It would be ideal if a suitable number of untreated cases of basilar artery insufficiency were available for follow-up study. Unfortunately, this syndrome has not been sufficiently recognized in the past and a search of our records for cases to be followed would be unrewarding. However, three syndromes have been recognized and diagnosed that are due to occlusion of the vertebral or basilar artery or their branches, and these are the syndromes of occlusion of the posterior inferior cerebellar artery, a branch of the vertebral; occlusion of the anterior inferior cerebellar artery,[12,13] a branch of the caudal end of the basilar artery; and occlusion of the superior cerebellar artery, the most rostral branch of the basilar artery.[14–17]

Closures of these arteries produce fairly characteristic clinical syndromes because of the presence of tracts in the midbrain, pons, and medulla which later become both crossed and uncrossed, producing a picture of mixed deficit partly on one side and partly on the other side of the body. We will not go into any detail on either the anatomy or symptoms of these syndromes. We hope to be able to do this in a later report.

In the past there has been little attempt to determine the outcome of thromboses of these arteries, although there have been hundreds of individual case reports and several excellent anatomic studies.[18–20] The largest series in any one report encompassed 28 patients, less than half of whom were followed for any considerable length of time.[21]

Therefore, it was decided to investigate the University Hospital records. From 1934 to 1957, a 23-year period, a total of 1,449 patients were thought to have suffered a nonhemorrhagic "cerebral" vascular thrombosis. Of these, 101 were suspected of having a thrombosis of one of the cerebellar arteries. After a careful check of the records and of the findings on follow-up neurologic examination, this number was reduced to 75. Of the 75, 62 were thromboses of the posterior inferior, 11 of the superior, and two of the anterior inferior cerebellar arteries. None of these was treated with anticoagulants. In all but two cases, these were strictly clinical diagnoses. Because of the small number and possible difference in prognosis in the last two categories, they are not included in the following detailed analysis of the 62 cases of thrombosis of the posterior inferior cerebellar artery. The 62 cases represented 4.3 per cent of the entire total of 1,449 nonhemorrhagic "cerebral" vascular episodes. There were 50 males and 12 females in the series, a ratio of 4 to 1, somewhat greater than the ratio of 2.3 to 1 in the entire group of 1,449. Thirteen of the 62 were alive and willing to return. They were examined, an interval history was taken, and the diagnosis was personally verified. (Others had been previously excluded from the series because the diagnosis could not be substantiated on follow-up examination.)

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TABLE 1

Follow-up Information on Entire Series of Patients with Thrombosis of the Posterior Inferior Cerebellar Artery

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	62	57	53	41	25	10	5
Number alive	60	52	41	22	7	3	1
Number dead	2	5	12	19	18	7	4
Per cent dead	3%	9%	23%	46%	72%	70%	80%

The average age of onset was 56 years, the median age 57. Table 1 shows the interval survival rate for the entire 62 patients. All patients were followed for at least a six-month period, but the total number of follow-ups decreased as the interval after onset increased. This is because the cases with recent onset could be followed only for a time as long as that from the onset to the present. We obtained some follow-up information on all of our patients, so the drop-off in follow-ups with the years is not due to failure to obtain information as to the ultimate outcome. As can be seen, the immediate death rate from posterior inferior cerebellar artery thrombosis is very low, but 46 per cent are dead in five years, 72 per cent in ten years, and 80 per cent in 20 years.

Forty patients, or 64 per cent of the series (table 2), showed evidence of other difficulties aside from their posterior inferior cerebellar artery thrombosis. This is not a new observation, and others have noted that a posterior inferior cerebellar artery thrombosis is merely a symptom of generalized arteriosclerosis.[19]

Tables 3 and 4 contrast the survival rate in patients who showed other evidences of disease that would tend to involve the vascular system with that of those who were without such evidence. This includes essential hypertension, diabetes mellitus, heart disease, and previous cerebral vascular episodes. The survival rate of those with evidence of other disease is the same as that found by other investigators in hypertensive patients with cerebral vascular thromboses.[22,23] With other disease the number dead at all intervals is slightly higher than that for the group as a whole: 52 per cent at five years and 100 per cent at 15 years. It is realized that the statistical significance of all these figures is rather low.

TABLE 2

Other Significant Diseases in Patients with Thrombosis of the Posterior Inferior Cerebellar Artery (Of a Total of 62)

	Number	*Per Cent*
Hypertension with and without hypertensive heart disease	20	50
Diabetes mellitus	9	22½
Arteriosclerotic heart disease	8	20
Previous cerebrovascular thrombosis	1	2½
Severe bronchiectasis	1	2½
Arteriosclerosis obliterans	1	2½
	40	100

Without other evidence of vascular disease, the percentage dead at five years has been reduced to 36 per cent and only one patient was dead at the end of a year.

The life expectancy in this disorder varies inversely with the age of onset. All patients were divided into groups according to their age at the time of the "stroke." Forty per cent of the 40 year old age group were dead five years after their posterior inferior cerebellar artery thrombosis (table 5), whereas normally the life expectancy would be 33 years for these people. Similarly, (table 6) of those that were 52 years old at the time of their "stroke," 44 per cent were dead in five years, when normally one would expect them to live 23 years on the average. Likewise, those that were between the ages of 56 and 65 at the time of their cerebellar artery thrombosis fared the same (table 7), with 40 per cent dead in five years, when they normally would live an average of 18 years. And lastly, (table 8) those who were over 65 at the onset showed a 70 per cent death rate in five years and 44 per

TABLE 3

Follow-up Information in Patients *with* Other Significant Disease
Average Age, 59 Years

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	39	36	33	27	15	4	0
Number alive	38	32	25	13	3	0	0
Number dead	1	4	8	14	12	4	0
Per cent dead	3%	11%	25%	52%	80%	100%	-

TABLE 4

Follow-up Information in Patients *without* Other Significant Disease
Average Age, 52 Years

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	22	21	20	14	9	6	3
Number alive	21	20	16	9	4	3	1
Number dead	1	1	4	5	5	3	2
Per cent dead	5%	5%	20%	36%	56%	50%	67%

TABLE 5

Follow-up Information in Patients Aged 32 to 45 with Thrombosis of the Posterior Inferior Cerebellar Artery

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	9	9	7	5	3	3	2
Number alive	8	8	5	3	1	1	1
Number dead	1	1	2	2	2	2	1
Per cent dead	11%	11%	29%	40%	67%	67%	50%

TABLE 6

Follow-up Information in Patients Aged 46 to 55 with Thrombosis of the Posterior Inferior Cerebellar Artery

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	17	16	16	14	9	5	1
Number alive	16	14	14	8	3	1	0
Number dead	1	2	2	6	6	4	1
Per cent dead	6%	13%	13%	44%	67%	80%	100%

TABLE 7

Follow-up Information in Patients Aged 56 to 65 with Thrombosis of the Posterior Inferior Cerebellar Artery

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	25	21	21	15	6	0	0
Number alive	25	21	17	9	1	-	-
Number dead	0	0	4	6	5	-	-
Per cent dead	0%	0%	19%	40%	84%	-	-

TABLE 8

Follow-up Information in Patients Aged 66 to 76 with Thrombosis of the Posterior Inferior Cerebellar Artery

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	11	11	9	7	6	2	2
Number alive	11	10	5	2	2	1	0
Number dead	0	1	4	5	4	1	2
Per cent dead	0%	9%	44%	71%	67%	50%	100%

cent were dead in two years, when normally they could expect to live 13 more years on the average.

What is the cause of death in these patients? Two of them died in the University Hospital, and postmortem examinations were done. Of the remainder, we relied on the statements of the relatives or the family physician or on the death certificate. Postmortem examination was done on only one of the patients who died elsewhere. About one-quarter died of heart disease, two-fifths of further cerebral vascular thromboses, and the remainder of various other or unknown causes (table 9). The fact that a quarter of these patients died of heart disease is substantiation of the thought that a posterior inferior cerebellar artery thrombosis is a sign of generalized arterial disease.

TABLE 9

Cause of Death in Patients with Thrombosis of the Posterior Inferior Cerebellar Artery (Of a Total of 62)

	Number	*Per Cent*
Further cerebrovascular accident	15	39
Coronary thrombosis	10	26
Suicide	4	11
Malignant neoplasm	1	3
Respiratory collapse	1	3
Unknown	7	18
	38	100

The 11 patients with superior cerebellar artery thrombosis were also followed (table 10). When this study began, it was felt that this syndrome might show a higher death rate than the posterior inferior cerebellar artery syndrome, because the basilar artery is the origin of the superior cerebellar artery and the involvement of the basilar artery might be thought to have a poorer prognosis than involvement of the vertebral, the origin of the posterior inferior cerebellar artery. However, our small series did not bear this out; two of the patients were still alive 19 and 21 years after thrombosis, and the one patient who died in eight days was found to have bilateral superior cerebellar artery thrombosis. Only three of the 11 did not have other evidence of vascular disease.

Two patients were diagnosed, both in retrospect, as having had a thrombosis of the anterior inferior cerebellar artery. This artery is also a branch of the basilar artery, and the progress of the one patient we have been able to follow closely is consistent with progressive involvement of that artery. He has had two worsening episodes in the four years since the onset. Anticoagulant therapy has been recommended in this patient.

TABLE 10

Follow-up Information on Patients with Thrombosis of the Superior Cerebellar Artery. Average Age at Onset, 51 Years. All Were Males.

Time interval of follow-up in years	½	1	2	5	10	15	20
Total number of patients followed for this interval	11	10	9	7	6	6	1
Number alive	10	9	8	7	6	5	1
Number dead	1	1	1	0	0	1	0
Per cent dead	9%	10%	11%	0%	0%	16%	0%

DISCUSSION

At the present time we do not feel that thrombosis of the posterior inferior cerebellar artery can usually be distinguished clinically from thrombosis of the parent vertebral artery. This is not a new thought, and we hope to be able to substantiate it in a later report. Therefore, it is likely that many patients with the clinical picture of a posterior inferior cerebellar artery thrombosis actually have a vertebral artery thrombosis. Yet they live an average of more than five years, a survival rate that is probably comparable to that of all "cerebral" thromboses in general,[22,23] and not to the short span that is usually thought to be associated with involvement of the vertebral-basilar system. To prove efficacious, anticoagulant therapy in patients with these syndromes should produce an average survival period longer than five years.

SUMMARY

A follow-up study has been made on all patients who have had a clinical picture of thrombosis of one of the cerebellar arteries. The following conclusions have been reached:

1. About 46 per cent of patients with thrombosis of the posterior inferior cerebellar artery are dead five years after the onset. Those with thrombosis of the superior cerebellar artery may survive even longer.

2. The death rate varies with the age of onset and with the presence of other evidences of vascular disease.

3. In general, with the possible exception of anterior inferior cerebellar artery thromboses, the course of the various cerebellar artery thromboses does not seem to be that seen in thrombosis of the basilar artery but more like that of cerebral thromboses.

4. If posterior inferior cerebellar artery thrombosis can be equated with thrombosis of the vertebral artery, then vertebral artery thrombosis (when manifested as a posterior inferior cerebellar artery syndrome) is not a rapidly progressive difficulty but should be regarded as any cerebral thrombosis when anticoagulant therapy is considered.

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Relapsing inclusion encephalitis (Dawson type) of eight years' duration

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SINCE DAWSON'S original reports[1,2] of intracellular inclusions correlated with a clinical encephalitis of insidious prolonged course, an increasing number of cases have been reported.[3–20] There is a stereotyped clinical course of progressive dementia, following initial behavior difficulty in a child.[21] Later there are myoclonic and choreiform movements, convulsions, optic atrophy or papilledema, and an eventual decerebrate state. Fever and other signs of infection are uncommon, although pyrexia often occurs terminally.

The usual course of the disease until death occurs is around six months to a year, or occasionally somewhat longer. One patient described by Malamud, Haymaker, and Pinkerton[6] lived seven years. An elevation in the spinal fluid colloidal gold curve often occurs, usually without a cellular reaction. A generalized episodic slow wave discharge in the electroencephalogram has been considered pathognomonic.[22,23]

The characteristic inclusion bodies may at times be difficult to find, but the histologic picture seems fairly uniform from case to case. Greenfield[7] has suggested that the absence of intracytoplasmic inclusions, the greater degree of white matter degeneration, and the Alzheimer cell changes in cases of long duration may be significant.

Many attempts to isolate a virus up to this time have been unsuccessful. Martin, Macken, and Hess[8] stated that a virus was isolated from their case but its exact nature was not defined. In one case of Foley and Williams[12] the herpes simplex virus was isolated but was presumed to be a contaminant on the basis of negative serologic tests.

All authors agree that Dawson's "inclusion encephalitis" is clinically indistinguishable from cases described pathologically as subacute sclerosing leukoencephalitis (van Bogaert). Many cases of leukoencephalitis have been described pathologically[5,9,16,17,24–42] and even more, clinically.[21,43] This disease seems to be especially prevalent in Europe. The general pathologic features of leukoencephalitis merge with those of cases in which inclusions were identified. In fact, two cases which were originally reported as subacute sclerosing leukoencephalitis were subsequently shown to have intracellular inclusions.[5,9,12,25] Moreover, in four cases[7,12,20] a cerebral biopsy showed subacute encephalitis without inclusions, while at subsequent necropsy inclusion bodies were identified.

Thus it appears that inclusions comprise a special feature of an otherwise fairly uniform clinicopathologic picture.[25] An unidentified virus was isolated in one case of leukoencephalitis.[9] Abnormally increased gamma globulin has been reported both in the cerebrospinal fluid and in the serum.[44] In recent years cases have been reported as subacute sclerosing leukoencephalitis, whether or not inclusion bodies were found. Leukoencephalitis is considered to have a close relationship to the panencephalitis of Pette-Doring, which is not limited to children,[25,45,46] and recently Glaser[18] noted two cases of subacute inclusion encephalitis in middle age.

Inclusion bodies in acute encephalitis have been proved to be related to the herpes simplex virus in seven reported cases.[47–53] Herpetic skin lesions may or may not be present. Clinically herpetic encephalitis has been identi-

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fied by the isolation of the virus from the spinal fluid and by a rising serum antibody titer,[53–60] or by cortical biopsy accompanied by serologic findings.[61,62] There are many cases with similar pathologic findings but without virologic studies.[63–68] A unique case of recurrent herpes simplex encephalitis associated with convulsive seizures was described by Bornstein and Ser.[69]

Acute encephalitis with inclusion bodies, presumably due to the herpes simplex virus, is, in general, clinically distinct from the cases of long duration. Although most pathologists[4,7,25,47,63,64,70] believe that the character and distribution of cellular inclusions in acute herpetic encephalitis is sufficiently distinct to indicate a different disease process from Dawson's encephalitis, Haymaker[71] and Krücke[19] believe that the two conditions may be closely related.

CLINICAL HISTORY

A ten year old white boy previously had been in good health and there was no family history of neurologic disease. In September 1947 he had a right-sided headache associated with mild pertussis infection. He began to do poorly in school, and by January 1948 personality changes, temper tantrums, and nocturnal fainting spells were noted. In March 1948 indistinct optic disk margins and diplopia for near objects were observed, along with slight enlargement of the blind spots. Spinal fluid examination was normal, as it proved to be throughout the subsequent course of the illness. The electroencephalogram showed a slow paroxysmal dysrhythmia with a left occipital focal trend. A pneumoencephalogram was normal. There was no significant fever at this time or later.

By July 1948 the child had lost weight and had begun to be clumsy with his hands, the left more than the right. There was stumbling, his speech was incoherent, and the electroencephalogram was more disordered, with high amplitude slow waves in the occipital leads. In August there were transient episodes of unconsciousness with sudden dropping of the head, and his behavior was worse, although a psychometric examination in October 1948 showed no definite organic deficit.

In November 1948 jerking seizures of the head and arms were first noted. There was transient improvement during the next month, accompanied by improvement in the electroencephalogram.

In January 1949 the child became dull and apathetic and developed a mixed aphasia. There was a right homonymous hemianopia and a mild right hemiparesis. Every few minutes massive jerking movements occurred in the right arm and leg. His speech was ineffectual, and he was unable to recognize his family. The electroencephalogram again became more disordered. Another pneumoencephalogram was normal.

In March 1949 the diagnosis of subacute encephalitis was established by cortical biopsy.[72] During the next three months there was progressive improvement concurrent with several courses of Aureomycin therapy. The seizures became less severe, and the child became alert, could count, complete simple sentences, and recognize the staff and his family. Later he was again able to walk without assistance. Sphincter control was regained. This improvement persisted for more than two years. The abnormal movements became reduced to a dipping adversive movement of the head to the right, with conjugate deviation of the eyes and stiffening of the right extremities. There was a mild spastic right hemiparesis and a homonymous hemianopia. Pallor of the right optic disk was first noted in 1951.

In late 1952 he gradually became unable to care for himself again and was readmitted to the hospital. His weight increased from 65 to 112 pounds during the ensuing months. He could again talk and walk short distances. Later in 1953 the abnormal movements disappeared.

During 1954 and 1955 his condition again became worse, and by August 1955 mental deterioration was severe. Both optic disks were pathologically pale and the homonymous hemianopia could not be clearly demonstrated. There was bilateral yellow macular degeneration and near the left macula was a small black zone of retinal degeneration. Spasticity was generalized. The electroencephalogram was characterized by fast and slow dysrhythmia, still without episodic slow bursts (figure 1A).

He became worse and was readmitted to the hospital with bronchopneumonia in December 1955, essentially decerebrate. The electroencephalogram was unchanged (figure 1B). A few weeks later the jerking movements of the right arm returned for the first time in two years. In February 1956 the pupils became dilated and fixed. Three days later respiration ceased.

CLINICAL SUMMARY

A ten year old boy showed behavior difficulties and developed mental deterioration insidiously. After a few months peculiar seizures appeared and papilledema was observed. Symptoms progressed irregularly over the course of a year. Rapid acceleration of the debilitation was manifested by signs of severe involvement of the dominant hemisphere. The diagnosis of subacute encephalitis was established at this time by cerebral biopsy. Concurrent with Aureomycin treatment there was improvement which continued for over two years. He then became worse, he was hos-

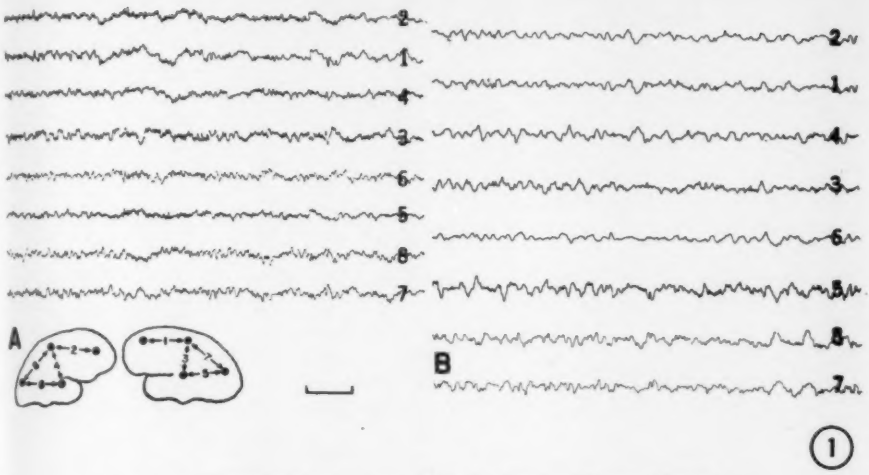

FIG. 1. *A*. Electroencephalogram August 1955. *B*. Electroencephalogram January 1956.

pitalized for ten months, and clinical improvement occurred again. His condition deteriorated over the next two years. He developed optic atrophy, macular degeneration, and finally died eight and one-half years after the onset of symptoms.

PATHOLOGIC STUDY

At autopsy the brain was atrophic (945 gm.), with a slightly thickened opaque arachnoid. The gyri were narrowed and the sulci widened, these changes being more marked in the occipital and parietal areas. The lateral ventricles were dilated. In coronal sections the centrum ovale was narrowed, especially in the occipital and frontal areas. The white matter was semitranslucent and depressed in relation to the adjacent cortex.

Microscopically, the arachnoid was thickened and infiltrated with lymphocytes and plasma cells. The centrum ovale of the occipital, parietal, and frontal regions was diffusely demyelinated, with some preservation of the short U fibers immediately beneath the cortex (figure 4). The white matter in the regions of degeneration was replaced almost entirely by a loose meshwork of fibrous astrocytes. Bilaterally in the occipital areas there were regions of spongy degeneration, with marked atrophy of both the cortex and white matter (figure 5). The cortex in all areas, and especially the occipital, was characterized by a great reduction in the number of neurons and by a severe gliosis (figures 2 and 3). The gliosis was, for the most part, comprised of swollen astrocytes, with occasional oligodendroglial cells and a moderate number of rodshaped microglial cells.

There was perivascular cuffing of many of the vessels chiefly by lymphocytes (figure 6). Many of the cortical vessels were larger in caliber than usual and had distinctly thickened walls. Satellitosis of residual neurons was present but minimal. In some areas there was calcific encrustation of neurons (figure 3). Similar changes occurred in the basal ganglia, thalamus, and midbrain but were, for the most part, less extensive and less severe. There was a spotty demyelinization of the optic nerves and chiasm. There was focal loss of cells in the ependyma lining the ventricles, and a granular ependymitis had resulted from projections of the subependymal glia.

The cerebellar cortex was normal. Diffuse but slight degenerative changes had occurred in the dentate nuclei, with glial nodules, neuronal degeneration, and some perivascular inflammation.

The changes in the medulla and spinal cord were striking and were apparently more re-

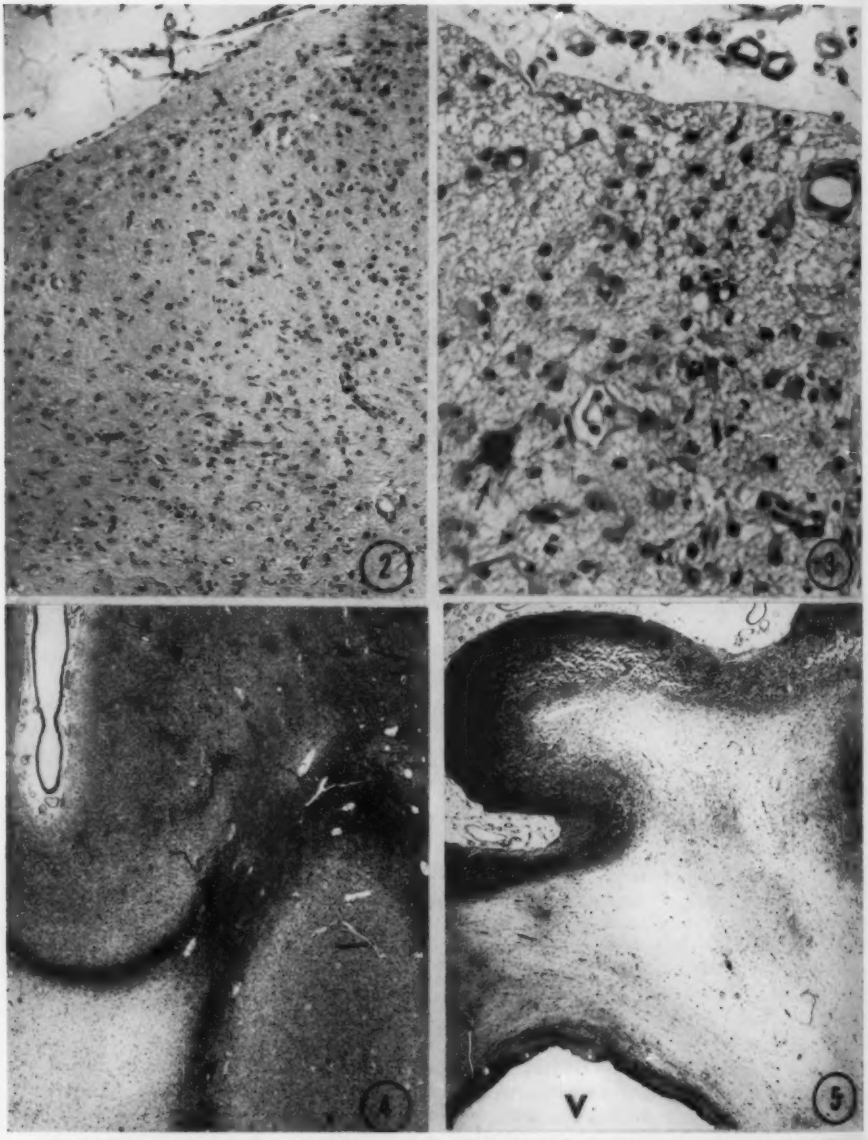

FIG. 2. Right motor area. There is a slight round cell infiltrate in the leptomeninges. The cytoarchitecture of the cortex is altered, with loss of most neurons and with a proliferation of astrocytes and rod-shaped microglia.

FIG. 3. Left parietal area. Small round cells are present in the subarachnoid space. The cytoarchitecture of the cortex is obliterated, with almost complete loss of neurons. An occasional neuron which has undergone calcific encrustation is present (arrow). The walls of blood vessels are increased in thickness. The predominant cellular element is the plump astrocyte.

FIG. 4. Weigert-stained section of left frontal area. Demyelinization is conspicuous in the centrum ovale, with preservation of myelinated fibers immediately beneath the cortex.

FIG. 5. Weigert-stained section of entire thickness of one region in the left occipital lobe. The occipital horn of the lateral ventricle is present at "V". The cortex is thin and completely replaced by glial cells. The extent of the narrowing and demyelinization is evident.

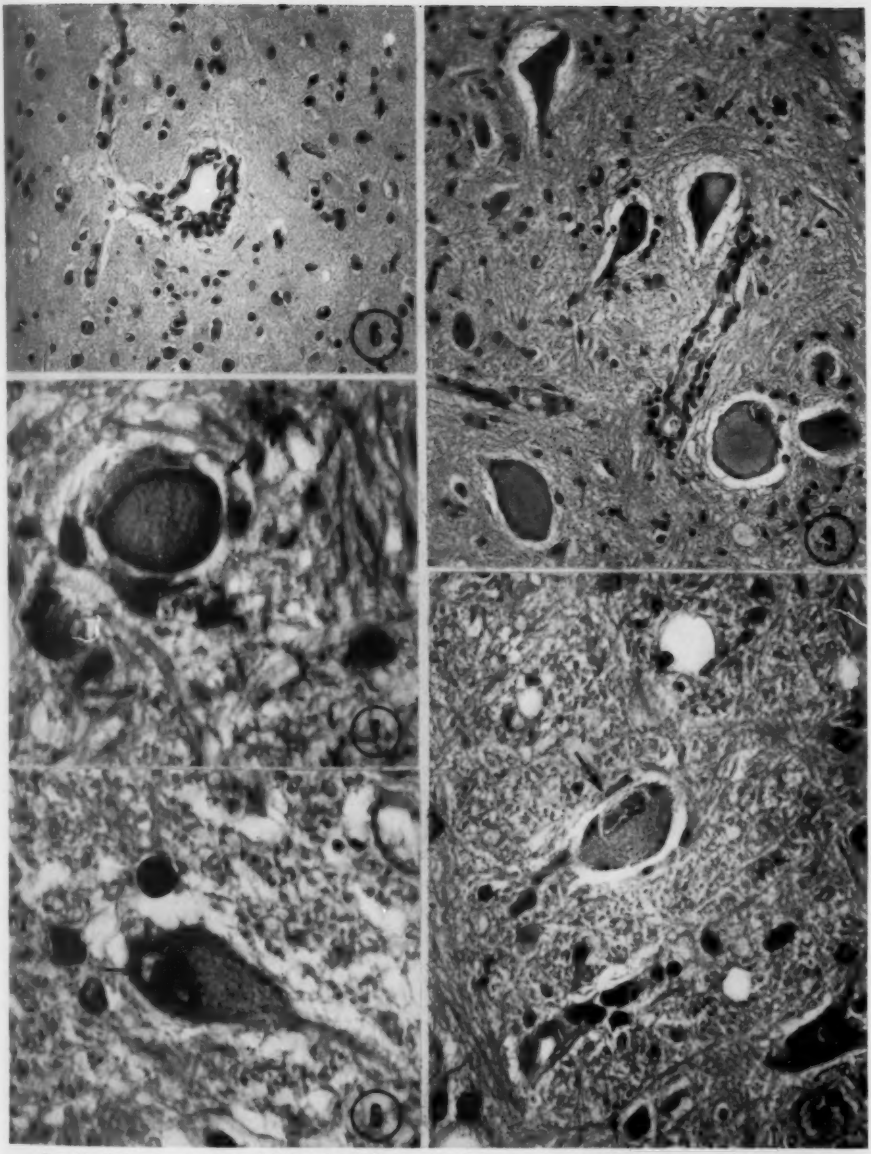

FIG. 6. Left premotor area. Perivascular infiltrate of lymphocytes and occasional plasma cells is present. Gemästocytic astrocytes and rod-shaped microglia comprise many of the adjacent cortical cells.

FIG. 7. A large rather homogeneous eosinophilic inclusion (arrow) completely fills the nucleus of a neuron and distorts its cytoplasm. The cytoplasm is present at the upper left. From the reticular substance of the medulla at the level of the inferior olivary nuclei.

FIG. 8. Neuron in anterior horn of spinal cord. A dense round inclusion (arrow) is present within the nucleus. A halo surrounds the inclusion.

FIG. 9. Anterior horn of spinal cord. Chromatolysis of neurons is prominent. The nucleus of the large neuron at the lower right contains an eosinophilic inclusion. Round cells have infiltrated about the vessels.

FIG. 10. Medulla. A neuron with a distinct intranuclear eosinophilic inclusion is present in the center of the field (arrow). A definite halo is present around the inclusion.

cent than those in the cerebrum. The pyramidal tracts and the restiform bodies were demyelinated. Throughout the medulla there were glial nodules, perivascular inflammatory infiltration of lymphocytes and plasma cells, and some proliferation of astrocytes. These changes were particularly marked in the floor of the fourth ventricle and in the inferior olivary nuclei. Lymphocytes had infiltrated about the vessels. The neurons were altered with an increase in surrounding satellite cells. A moderate number of the neurons had inclusions (figures 7 to 10), usually nuclear and occasionally intracytoplasmic. The eosinophilic inclusions generally did not completely fill the nucleus and were surrounded by a halo (figure 10).

In the spinal cord the lateral columns and, to a lesser extent, the ventral corticospinal tracts were demyelinated. The most striking changes in the spinal cord were in the anterior horns. In these regions there were distinct perivascular inflammatory infiltrate, increase in neuronal satellite cells, and focal accumulations of glial cells. The neurons were altered to varying degrees. Some were greatly distorted, with obvious chromatolysis (figure 9). In others there were noted either nuclear or cytoplasmic eosinophilic inclusions (figures 8 and 9).

With the exception of a dysplastic kidney on the left, acute pyelonephritis of the right kidney, and a diffuse bronchopneumonia, the other organs were normal.

DISCUSSION

This case most closely resembles case 3 of Malamud, Haymaker, and Pinkerton.[6] Their patient lived for seven years after the onset of symptoms and also had macular degeneration. This lesion occurred early in the course of the illness and resulted in an initial diagnosis of cerebromacular degeneration. The distinct periods of remission, which seem to characterize Dawson's encephalitis of long duration, are unexplained.

The electroencephalograms of this patient never demonstrated the generalized episodic paroxysmal slow waves described by Radermaker[22] and by Cobb and Hill.[23] In fact, the diagnosis in the present case was questioned[73] on the ground that this electroencephalographic finding was not present. Such episodic slow waves were not described by Akelaitis and Zeldis,[3] nor by subsequent authors.[9,12,13] Furthermore, we have not seen them in another case of inclusion encephalitis[10] which followed a more typical subacute course (O'Leary, unpublished). Several investigators have indicated that the episodic pattern may not be present throughout the illness and may be missed unless records are made at frequent intervals. Thus, although it may be true that the "specific" electroencephalogram occurs only rarely with other disease entities,[74–77] it may not always be present in cases of inclusion encephalitis.

As mentioned above, this is the fifth case in which inclusion bodies were discovered at necropsy but were not seen previously at cortical biopsy. It is possible that inclusions are a late pathologic development in this disease, even though they develop rapidly in acute herpetic encephalitis. It is equally possible that the amount of tissue available at biopsy was insufficient or was from a portion of the cortex in which the inclusions were not present.

In this prolonged case of inclusion encephalitis, inclusions were numerous in the spinal cord and medulla. An occasional inclusion was still evident in the cortex of the hippocampus, but they could not be recognized elsewhere in the cortex. Their scarcity in the cortex is probably correlated with the paucity of neurons still present and reflects more recent involvement of the medulla and spinal cord. Further evidence pointing to the continued progression of the inflammatory process and the degenerative changes is the widespread inflammatory infiltrate about the blood vessels in all parts of the central nervous system.

The far advanced demyelinization in this case points out the close relationship of the morphologic findings in the chronic inflammatory diseases of the nervous system and in the chronic demyelinating diseases, so that terminally it may be difficult to distinguish one from the other.

SUMMARY

A case of inclusion encephalitis is described, in which a relapsing clinical course lasted eight and one-half years, the longest duration yet reported. Biopsy in the second year demon-

strated only subacute encephalitis. Clinical, electroencephalographic, and pathologic findings indicate a progressive inflammatory reaction, with chronic damage in the forebrain and a more active process in the brainstem and spinal cord. This case was originally reported in 1952[72] as one of subacute encephalitis with remission.

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Progressive cerebral degenerations of childhood

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RECLASSIFICATION of the syndromes of cerebral degeneration in childhood is being impelled by rapidly expanding interest in pediatric neurology, by the emergence of medical genetics, and by specific discoveries in neurochemistry. The resounding eponyms for these syndromes, such as Pelizaeus-Merzbacher, Bielschowski, Spielmeyer-Vogt disease, and the like, are yielding to more logical and appropriate desgnations. Characteristic genetic patterns have been disclosed that introduce some order into this nosologic chaos and also provide a firmer basis for counseling parents of the afflicted child.

Considerably more collation of data is required in this neglected field before inferences useful to the clinician can be offered. At present, the onset of progressive deterioration and neurologic defects in a previously healthy child poses a perplexing diagnostic problem. The pediatrician or neurologist is often skeptical of the mother's story that the child was healthy at birth and developed normally. Rather, the conclusion often is erroneously made that a pre-existing birth injury became manifest as the child grew older. A greater awareness that regression due to progressive degenerative disease can occur might increase the frequency with which these conditions are diagnosed and reported, and greater familiarity with these syndromes might motivate more clinicians to pursue the study of the individual case to a finite etiologic diagnosis.

The semeiology of this group is more or less uniform. In addition to the history of truncated development or regression and frequently of epileptic attacks, the neurologic examination reveals mental retardation, pyramidal tract signs, and often visual impairment with optic atrophy. Refinement of the diagnosis is dependent largely on laboratory studies.

A sequential program of tests is offered, beginning with the simplest, that is, the urinalysis which would identify or exclude the following: 1) Galactosemia, in which the reducing substance in the urine, if present, is tested further for galactose. 2) Phenyl pyruvic oligophrenia; a green color with acidified ferric chloride is commonly pathognomonic. 3) Cytomegalic inclusion disease, which may be diagnosed by finding desquamated renal tubule cells containing nuclear or cytoplasmic inclusions. 4) Metachromatic type of diffuse sclerosis; red metachromatic granules can be demonstrated in the urine sediment stained with aqueous toluidine blue.

Roentgenographic examination of the skull would further identify: 1) Cytomegalic inclusion disease, which often reveals fine punctate calcifications in the position around the lateral ventricles. 2) Toxoplasmosis, with more diffuse parenchymatous calcification. Skin and dye test would confirm the diagnosis.

The electroencephalogram is of value in the diagnosis and particularly in prognosis. Hypsarhythmia, a fairly common finding in this group, presages progression, deterioration, and also difficulty in controlling the seizures. Alternating sleep spindles are associated with hydrocephalus, and focal abnormalities may suggest proencephaly or other cerebral malformations.

The pneumoencephalogram would exclude certain congenital malformations and would reveal cerebral atrophy or hydrocephalus.

Brain biopsy, a final diagnostic measure, is reserved for a few selective cases but may

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FIG. 1. *Case 1.* Photograph of the patient at the age of 28 months. She is irritable and unable to sit up or to roll over.

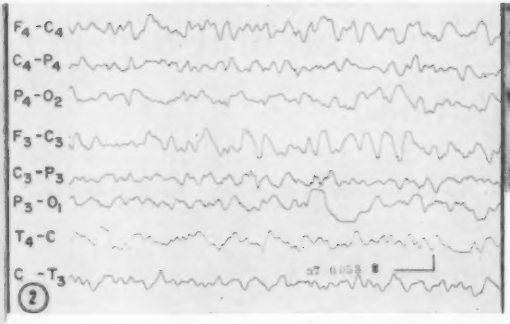

FIG. 2. *Case 1.* Electroencephalogram at the age of 28 months shows a generalized slow wave dysrhythmia.

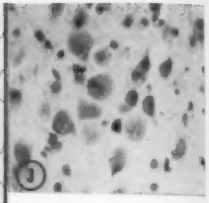

FIG. 3. *Case 1.* Biopsy of the cortex. The neurons are greatly distended with abnormal lipid accumulation. Nissl stain.

be justified more often than is employed in this group. An example of this follows.

Case 1. This was an only child of young, healthy parents. The family history was noncontributory. The pregnancy and birth were normal. The infant was healthy in all respects and was developing normally until 11 months of age, at which time she was able to walk holding a railing, say "mama" and "dada," and wave "bye-bye." From that time on her development slowed considerably, and she never achieved walking on her own. A progressive deterioration of mental and motor function soon became evident, and at the age of two years she was unable to speak or sit unaided. A pneumoencephalogram performed at the age of 28 months disclosed a symmetric ventricular system of normal size. The cerebrospinal fluid protein was 50 mg. per cent and there were three cells per cc. On physical examination at the age of three and one-half years, she was apathetic and irritable. All extremities were very weak, and she was unable to roll over (figure 1). Signs of pseudobulbar palsy were present, and an exaggerated response to startle could be elicited. Funduscopic examination revealed normal disks, maculae, and retinae. The rest of the physical examination was negative.

Routine laboratory examination of the blood and urine was normal. Tests for phenylpyruvic acid, galactose, and toxoplasmosis were negative. An electroencephalogram showed diffuse dysrhythmia of slow type (figure 2). The clinical impression at that time was diffuse sclerosis or cerebral lipidosis, with subacute inclusive body encephalitis to be excluded. The parents preferred a definite diagnosis to guide them in deciding whether they wanted future offspring. They agreed readily to a brain biopsy, and a piece of cortex measuring 1 by 1 by 1 cm. was removed from the right frontal lobe. The circular bony plate which was removed with the trephine was reinserted.

Histologic examination revealed the presence of cerebral lipidosis. In Nissl stain preparations some neurons were disintegrated and the others were distended with granular material which stained scarlet red with Sudan III and IV in frozen sections (figure 3). The patient was seen again at the age of four years. At that time she showed marked generalized spasticity and exhibited numerous epileptic attacks of both focal and tonic types. Her optic disks were pale, but otherwise the maculae and retinae were not remarkable.

Although a clinical diagnosis of diffuse sclerosis was considered as most likely, the brain biopsy had to be resorted to in order to reveal the definite pathologic diagnosis. As occurred frequently in the other cases, there was lack of correspondence between clinical syndrome and the histologic picture. Further, in this patient more practical assistance to the parents was possible only by the more complete knowledge of the pathologic process. This guided them in deciding in favor of adoption rather than further procreation.

The following two cases are further examples of this group. They also represent the unsettled question of whether the frequent seizures usually present are in themselves responsible for causing or accelerating the deterioration. These cases suggest that the primary

process is the probable cause of both the deterioration and the seizures.

Case 2. A boy aged two years and nine months had two maternal aunts known to have epilepsy; otherwise the family history was negative. The pregnancy and delivery were normal, and the infant's development was uneventful until three months of age, at which time he developed convulsions for the first time. These were not associated with fever or illness. From then on he continued to have frequent epileptiform attacks, mainly of minor type, until he was 10 months of age. His development during this period progressed very little. For no apparent reason he was free from epilepsy between 10 and 16 months of age, during which time his development progressed considerably. He learned to walk and say a few words. However, with the recurrence of seizures at the age of 16 months, the already acquired functions began to deteriorate. He was given anticonvulsant medication, but his attacks could not be controlled satisfactorily. He continued to have an average of five to seven attacks per week, usually in groups. Most of the attacks consisted of rapid extension movements of both arms above his head and deviation of eyes and head to one side, mainly to the left. If he happened to be standing, his body would tremble and he would reach for support. The duration of a single attack was five to 15 seconds. Generalized convulsions also occurred but they were less frequent than the other attacks.

Examination at the age of two and one-half years showed a physically well-developed boy who was able to walk fairly well. However, he showed no speech and no comprehension. His vision and hearing were considered to be normal. He was quite restless and had to be under constant surveillance because of destructiveness.

Apart from slightly deficient skill in the use of his hands, the motor system was normal. He perceived sensory stimuli and there was no evidence of cerebellar incoordination. The tendon reflexes were normal. The retinae, the disks, and the maculae were also normal.

Routine laboratory tests of blood and urine disclosed no abnormalities. Tests for phenylpyruvic acid, galactose, and toxoplasmosis were negative. Roentgenograms of skull and skeleton were normal. The electroencephalogram revealed a marked diffuse abnormality. The background activity consisted of poorly organized four to five per second waves. Epileptiform discharges were almost continuous, resembling the patterns described by Gibbs as hypsarhythmia. The pneumoencephalogram showed a symmetric ventricular system of normal size.

The tentative clinical diagnosis was epilepsy of infantile spasm type, with mental deterioration. It is of interest that his development progressed rapidly during the time when he was free of epileptiform attacks, only to regress subsequently with the recurrence of seizures.

Case 3. Both parents are healthy and there is no history of nervous or mental disorders in their families. The patient is their only child. The pregnancy was normal, and the birth uneventful. Development was satisfactory in all respects until 20 weeks of age, when the infant began to have multiple epileptic attacks. These consisted of sudden stiffening of the body and extension of both arms above the head. He would have several such attacks in succession, eight to ten times daily. Anticonvulsant therapy afforded only slight decrease in the frequency of these spells. His development did not progress, and, in fact, he lost most of his initial accomplishments.

Examination at the age of one year showed a slightly obese, apathetic boy who remained immobile most of the time (figure 4). He responded to painful stimulation with an increase in random motor activity and with a brief cry. There was generalized muscular weakness but no localized paralysis. All tendon reflexes were brisk and equal. Plantar responses were equivocal. Moro response could not be elicited. Funduscopic examination disclosed normal disks and retinae. He responded to visual and auditory stimulation. Routine laboratory tests were normal. Tests for phenylpyruvic acid and toxoplasmosis were negative. Protein-bound iodine was 5.1 micrograms and fasting blood sugar was 87 mg. per 100 ml. Radiologic examinations of skull and skeleton were normal. An electroencephalogram disclosed a diffuse abnormality. There were multiple epileptiform discharges, bilaterally synchronous and of diffuse focal origin. The cerebrospinal fluid showed normal constituents. Subdural taps were negative. The pneumoencephalogram showed slight, symmetric dilatation of the ventricular system. He

FIG. 4. *Case 3.* At the age of 11 months the patient is unable to sit up or to roll over and is irritable.

FIG. 5. *Case 4.* Pneumoencephalogram discloses a slight, symmetric dilatation of the ventricular system.

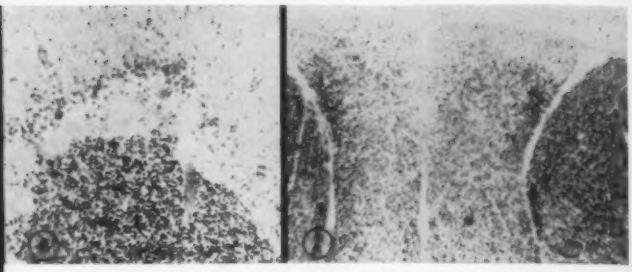

FIG. 6. *Case 4.* Marked loss of Purkinje cells with associated proliferation of the Bergman glia. The number of granule cells is decreased.

FIG. 7. *Case 4.* The posterior columns of the spinal cord show pronounced demyelination.

was given consecutively all available anticonvulsant medication up to the tolerance dose, both singly and in combination, but at best his attacks could be decreased only to two or three a day, each consisting of three to seven massive spasms. He was seen again at the age of 20 months, at which time his condition had changed very little. He was fretful and had marked generalized weakness. Funduscopic examination disclosed pallor of disks. The clinical impression was that the patient suffers from cerebral degeneration (diffuse sclerosis, lipidosis) or functional deterioration as a result of epilepsy. Further refinement of the diagnosis has not been possible.

The next case testifies further to the unreliability of clinical phenomena in establishing etiologic diagnosis in progressive cerebral degeneration, emphasizing the frequent disparity between clinical inferences and histopathologic data.

Case 4. A three year and ten month old white boy had a normal birth and family history. Two younger siblings are normal. The initial development until 12 months of age was satisfactory. At the age of one year eversion of both feet and ankle weakness were noted. However, he began to walk a few steps without aid at 17 months. At 18 months his vision began to deteriorate and bilateral optic atrophy was diagnosed. His vocabulary then consisted of about 12 words. A pneumoencephalogram performed at that time showed slight enlargement of the ventricular system (figure 5). At the age of three years he began to have difficulty with balance, and his hands exhibited tremors on attempting to grasp an object. During the subsequent six months his condition deteriorated further and frequent focal convulsions began in the right thumb. In addition, there were isolated asymmetric muscular contractions of

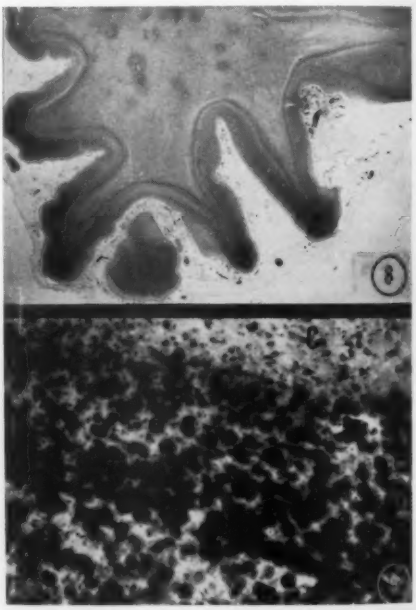

FIG. 8. *Case 5.* Brain section stained for myelin shows extensive demyelination of the central white matter.

FIG. 9. *Case 5.* Frozen section which includes part of the cerebral cortex (C) and the adjacent white matter stained by toluidine blue method. The cortical neurons are relatively well preserved. The subcortical white matter consists of densely packed clumps of metachromatic material.

myoclonic type occurring in all extremities and in the facial muscles. He became incontinent and lethargic. Funduscopic examination showed pallor of disks, grey and slightly elevated maculae, and, by contrast, pinkish-appearing fovea. Response to light and auditory stimulation was grossly deficient. The patient's condition deteriorated, and he died in respiratory failure at the age of three years and ten months. The clinical findings were consistent with cerebral lipidosis.

Postmortem examination showed pneumonitis and bronchial obstruction. On gross inspection the only abnormality of the brain consisted of a moderate degree of atrophy of the cerebellar folia. Histologic examination disclosed the following findings: 1) degeneration of ganglion cells in the retina, without evidence of lipid deposition; 2) demyelination of both optic nerves; 3) degeneration and disappearance of Purkinje and granule cells in the cerebellum, but again without the presence of sudanophilic material (figure 6); and 4) demyelination of the posterior column in the spinal cord (figure 7). The pathologic diagnosis was an infantile form of cerebellar ataxia.

Case 5. A three and one-half year old white boy had a noncontributory family history. The pregnancy and birth were normal. He was a healthy child in all respects until two years of age, when he developed convulsions. Examination at that time disclosed a mild generalized weakness and slight apathy. Radiograms of the skull and an electroencephalogram were normal. His condition continued to deteriorate progressively. At the age of three years he was unable to walk and showed little interest in his surroundings. He had generalized weakness, and his tendon reflexes were unobtainable. Funduscopic examination showed pallor of the disks but no other abnormality. Pneumoencephalogram disclosed slight, symmetric dilatation of the ventricular system. The total protein in the cerebrospinal fluid was elevated to 85 mg. per 100 ml. The electroencephalogram showed diffuse dysrhythmia. Diagnosis of progressive cerebral degeneration was considered. At three years and three months he became bedridden and unresponsive, requiring full-time nursing care. Death occurred at three and a half years of age in a state of emaciation.

Postmortem examination disclosed bronchopneumonia and fatty degeneration of the liver. On gross inspection the brain showed a moderate degree of atrophy. On sectioning, the white matter was found to be hard and diffusely demyelinated. Histologic studies revealed metachromatic type of diffuse sclerosis with relatively well preserved nerve cells (figures 8 and 9).

Again, this demonstrates a more or less stereotyped clinical pattern and course, with a precise diagnosis established only at autopsy. Urine studies were not done but might have been positive for granular metachromatic bodies.

SUMMARY

Progressive cerebral degeneration is a clinical syndrome without a unitary pathologic process. The older eponyms should be abandoned and a reclassification attempted in light of a newer knowledge of genetics, histopathology, and biochemistry. Five illustrative cases are presented in this preliminary report. Differential diagnosis and sequential pattern of tests are offered.

Precise diagnosis would permit accumulation of useful data on the diverse mechanisms of progressive cerebral degenerations in childhood.

Further, genetic counseling could be offered to the parents in some instances.

Clinical and electroencephalographic effects of Megimide in patients without cerebral disease

Martin A. Green, M.D., and Max Fink, M.D.

FOLLOWING the introduction of Megimide (beta, beta methylethylglutarimide) as an antagonist for barbiturate intoxication in 1955, considerable interest has been stimulated in its clinical applicability. Initial reports noted its efficacy in barbiturate poisoning,[1–4] but subsequent studies failed to substantiate this application.[5–8] In this laboratory, barbiturates are frequently administered under the standardized conditions of the "amobarbital test."[9] It was thus possible to assess the efficacy of Megimide in altering the behavioral response of human subjects to physiologic equivalent amounts of barbiturate.

In addition to its suggested antagonism to barbiturate, Megimide induces both paroxysmal discharges in the electroencephalogram and clinical grand mal seizures.[10–14] The present report concerns our experience with both the behavioral and electroencephalographic effects of Megimide.

MATERIAL AND METHODS

Thirty-four hospitalized voluntary psychiatric patients with psychoneurosis, depression, or schizophrenia, ranging in age from 27 to 64 years, were studied. Megimide in a concentration of 5 mg. per cc. was administered intravenously at the rate of 0.5 mg. per kg. per minute, until definite changes were observed in the electroencephalogram and often beyond this point. The amount of Megimide varied from 45 mg. to 250 mg.

In 15 subjects Megimide was administered without prior amobarbital. In 19 patients it was given following the administration of intravenous amobarbital which was injected at 0.5 mg. per kg. every 40 seconds, in amounts necessary to induce nystagmus, slurred speech, and marked drowsiness or sleep.

All experiments were undertaken in the electroencephalographic laboratory. An electroencephalogram was made prior to the injections and was run continuously during the administration of both drugs. The electrode placement consisted of frontal, motor-parietal, occipital, anterior temporal, posterior temporal, vertex, and earlobe. Both scalp-to-earlobe and scalp-to-scalp combinations were used.

RESULTS

The electroencephalogram in all subjects prior to the administration of the drugs was "normal," that is, symmetric and non-dysrhythmic.

Electroencephalographic Response

In the amount and rate of injection of Megimide employed, electroencephalographic changes occurred in every patient. The type of response and the amount of drug necessary to induce such a response were highly variable. The electroencephalographic changes included irregular low- and moderate-voltage slow activity, bursts of slow activity (usually of high voltage), single spike discharges, and spike-wave forms (figure 1 A, B, and C). These effects were diffuse and symmetric, with greatest prominence in the temporal leads.

The sequence of these responses was inconstant. Irregular, low-voltage slow activity was the most frequent initial change in the record. In other instances, bursts of high-voltage slow activity or spike activity appeared initially. As the injection continued, the amplitude and per cent time delta activity in-

From the department of experimental psychiatry, Hillside Hospital, Glen Oaks, Long Island, New York.
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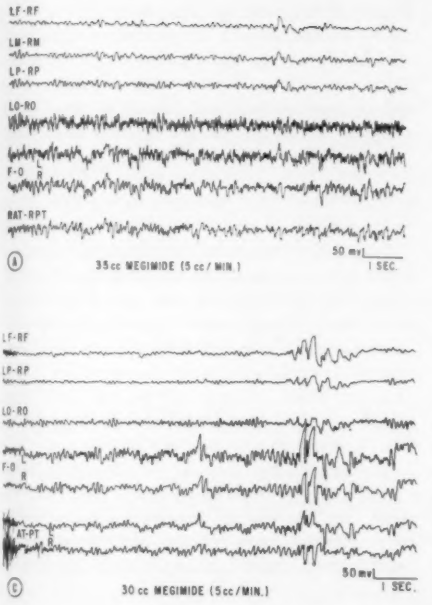

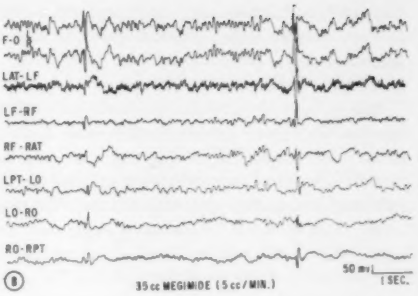

FIG. 1. Different types of electroencephalographic response to Megimide. *A*, delta activity, irregularly and in bursts, *B*, single spike activity, *C*, spike-wave activity

creased. Bursts of high-voltage slow activity were seen eventually in almost all patients. Spike discharges, however, were less frequent, even with relatively large doses of Megimide. For example, the tracings in one subject after receiving 220 mg. of Megimide and in another after receiving 250 mg. showed irregular diffuse slow activity without spike activity.

Seizures

Because of the nature of the population and the goals of our study, we specifically avoided administering Megimide in rates and amounts that would produce clinical grand mal seizures. Despite these precautions, a grand mal seizure was inadvertently induced in one patient. A 33 year old woman was given 200 mg. of Megimide at the rate of 50 mg. per minute. Up to 150 mg. there was only a decrease in the voltage of the alpha activity. After 200 mg. there was a sudden long run of diffuse, rhythmic 4 to 5½ cycles per second high voltage activity, with intermixed spike activity which was immediately followed by the seizure. The electroencephalogram during injection and prior to the seizure showed minimal changes, and the seizure was not anticipated

Subjective Response

The subjective reaction to Megimide was minimal, even when the induced changes in the electroencephalogram were severe. A few subjects complained of nausea, "dizziness," "shakiness," or a peculiar sensation in the abdomen. It was possible, however, to continue the injection without further increase in the symptoms. Two subjects became apprehensive, and in one of these the injection had to be discontinued.

Myoclonic jerks occurred frequently. They were usually mild and confined to one extremity. Less frequently they were bilateral and more severe. The relationship between these movements and spike activity was inconstant. The myoclonic jerks usually preceded the appearance of spike activity, although the reverse occurred occasionally. The simultaneous appearance of spike activity with myoclonic jerks was infrequent.

The effect of Megimide was short-lived. There were no instances of seizures or other abnormal responses later in the day following its administration. However, since intravenous amobarbital followed in all patients, this may have prevented such occurrences.

The clinical and electroencephalographic responses to intravenous amobarbital following Megimide appeared similar to those seen in subjects in whom amobarbital is administered without prior medication. The slow-wave or spike activity induced by Megimide disappeared and the usual patterns associated with barbiturates developed (figure 2). However,

the well-modulated high per cent time beta activity usually noted after barbiturate administered was less prominent.

Megimide Following Amobarbital

One group of subjects received intravenous amobarbital prior to Megimide until drowsiness, slurred speech, and nystagmus were induced. The electroencephalogram showed the patterns commonly associated with barbiturates, that is, an increase in voltage and per cent time fast activity and a decrease in amount and voltage of alpha activity. The most prominent clinical change was the awakening of the subject. Within the few minutes necessary for the injection, the patient became more responsive, slurred speech disappeared, and drowsiness, both on subjective and objective evaluation, was minimal or absent. Nystagmus became inconstant, unsustained, or disappeared completely. Gait, including heel-to-toe walking, was steady. However, the awakening effect was not uniform for all aspects of behavior altered by barbiturate. For example, if the subject became euphoric and more talkative with barbiturate, such behavior may have persisted in a milder form, even after the drowsiness of amobarbital was abolished by Megimide.

These clinical changes were accompanied by alterations in the electroencephalogram (figure 3). Patterns of drowsy activity disappeared. Alpha activity increased both in amount and voltage. Fast activity induced by amobarbital usually persisted unchanged or was reduced only sightly. In some instances it increased in amount and voltage. The prior administration of amobarbital did not prevent the appearance of paroxysmal discharges. Bursts of high-voltage slow activity, spike activity, or spike-wave activity often appeared, usually during or after awakening. Such activity was not a necessary accompaniment of the awakening response, however, since other subjects in whom clinical drowsiness disappeared did not show such discharges.

DISCUSSION

Megimide is similar to pentalenetetrazol (Metrazol) in that it induces delta activity, spike and spike-wave activity in the electroencephalogram, and clinical grand mal seizures. Such changes occur in nonepileptic subjects without brain disease, and considerable individual variability in the threshold for these changes exists. These discharges are nonspecific and cannot be used as evidence of the presence of a seizure disorder.

The possibility of using Megimide in activating the electroencephalogram has received study.[10–12] Several investigators have noted a more gradual onset of the electroencephalographic and clinical changes with Megimide than with Metrazol. For this reason, the opinion is expressed that Megimide may be more facile in reproducing both clinical and electroencephalographic seizures in patients with seizure disorders. It should be emphasized, however, that in the one patient in the present study in whom a grand mal seizure occurred, the seizure began suddenly and was not anticipated either from the electroencephalogram or previous clinical responses.

Megimide is effective in counteracting the clinical effects of small doses of intravenous amobarbital. This property has been previously demonstrated in animals[9] and is being utilized

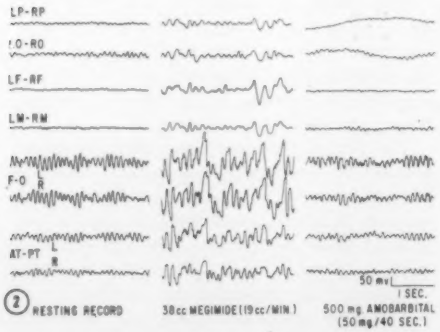

FIG. 2. Effect of amobarbital following administration of Megimide

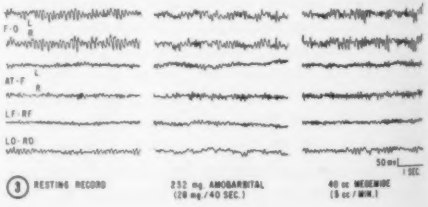

FIG. 3. Effect of Megimide following administration of amobarbital

in anesthesiology to shorten the recovery period from barbiturate anesthesia postoperatively.[15] It is questionable whether this action is specific for barbiturates or whether it also applies to states of altered consciousness due to other agents as well.[16]

CONCLUSIONS

1. Thirty-four psychiatric patients without cerebral disease were given Megimide (beta, beta-methylethylglutarimide) before and after the administration of intravenous amobarbital.

2. Megimide produces irregular delta activity, bursts of delta activity, and spike and spike-wave activity in the electroencephalogram. Such effects are similar to those produced by pentalenetetrazol (Metrazol).

3. Considerable individual variability exists in the amount of drug necessary to produce these changes.

4. A grand mal seizure was inadvertently induced in one patient. The electroencephalogram during the injection and prior to the seizure showed minimal changes and the seizure was not anticipated.

5. Megimide counteracts the clinical and some of the electroencephalographic effects of small doses of intravenous amobarbital.

Megimide supplied through the courtesy of A. & J. Nicholas Ltd., Slough, Bucks, England.

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■ Sometimes epilepsy makes its attack without having been preceded by this or any other premonitory symptom, when the patient falls suddenly to the ground in a state of utter insensibility. He neither sees, nor hears, nor is at all conscious of impressions, however powerful they may be. The most violent stimulants produce no effect. Voluntary motion is entirely abolished, the muscles being no longer obedient to the will, or rather the will being no longer in action. Involuntary muscular power, however, remains, and is indeed excessive, and sometimes preternaturally violent.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Tilt table electroencephalography in insufficiency syndromes

Stuart Weiss, M.D., and Wolfgang Froelich, M.D.

PRIOR TO THE ORIGIN of the present concept of cerebrovascular insufficiency, Kubick and Adams[1] described the syndrome of thrombosis of the basilar artery and this led to other confirmation.[2,3] The syndrome of occlusion of the carotid artery was also documented more extensively.[4] Many cases reported had a history of prodromal episodes of recurrent neurologic deficit of sudden onset and brief duration, with periods of normalcy between, suggesting the need for further understanding of the cerebrovascular dynamics which underlay them.

Millikan and Seikert,[5,6] in reviewing cases of carotid and basilar insufficiency, stressed the multiplicity of symptoms which may precede stenosis of these vessels and suggested that there may be difficulty in distinguishing between carotid and basilar syndromes. Denny-Brown[7,8] and Meyer and co-workers,[9] emphasized the focal aspects of the problem. After reviewing evidence for vasospasm, Denny-Brown ascribed the intermittent symptoms to failure to maintain the collateral circulation of a compromised area of the brain due to "systemic hemodynamic crises," noting that a drop in blood pressure was frequently associated with the onset of transient neurologic deficit. Corday and Rothenberg[10,11] defined cerebrovascular insufficiency similarly, this view being supported by the pathologic studies of Hicks and Shields.[12] The latter were unable to find evidence favoring mechanical occlusion in 60 of 100 cases, which suggests that these cerebrovascular accidents had resulted from failure of the systemic circulation.

Others have demonstrated that thromboses of cerebral vessels can occur without infarction.[13] Hultquist[14] (quoted by Murphy[15]) described a series in which only one-third of the patients with carotid thromboses showed cerebral infarcts. These findings and the moderate to marked improvement in neurologic deficit which can be seen within a short time after thromboembolic or thrombotic occlusion of large cerebral vessels could be explained by the presence of a collateral network of cerebral vessels, large and small. Angiographic evidence for the existence of a potential collateral circulation in patients with thromboses of the internal carotid has been presented also.[16] This is by way of the connections between anterior and posterior communicating arteries (circle of Willis), but anatomic variations may render this circulation inconstant. Other anastamoses between internal and external carotid branches and meningeal branches of anterior, middle, and posterior cerebral arteries have also been described. The latter are similar to those which Welch and co-workers[17] observed in the angiograms of patients with occlusion of the middle cerebral artery.

In experimentally produced occlusion of major vessels, the largest immediate adjustments in collateral circulation are made through dilatation of smaller arterial anastomoses, resulting in increased tissue oxygen availability in the marginal area of ischemia.[18] Maintenance of blood pressure over 50 mm. Hg and inhalation of pure oxygen are other factors which tended to decrease the size of the ischemic area. These changes were thought to be independent of the sympathetic innervation, since they were not influenced by sympathectomy or by stellate ganglion removal.[19]

Widening recognition of the significance of the insufficiency syndromes as prodromata to arterial stenosis[5–8] has shifted the emphasis in cerebrovascular disease from rehabilitation after the accident to prophylactic measures to maintain the best possible cerebral circulation. Fisher and Cameron[20] and Millikan, Siekert,

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and Schick[21–23] used anticoagulant drugs successfully in treating carotid and basilar insufficiencies and partial progressive basilar occlusion. The follow-ups were of short duration. Millikan and co-workers[22] also mentioned a definitely higher mortality in patients with basilar occlusive disease who were not treated with anticoagulant drugs. Meyer and co-workers[24] used the tilt table electroencephalogram to evaluate the efficacy of anticoagulant therapy, pressor agents, and oxygen. Their results generally supported previous clinical impressions of the value of these agents in preventing the insufficiency syndrome.

Successes with anticoagulant therapy point up the importance of early clinical diagnosis in vascular insufficiency and suggest the need for a confirmatory test which is reliable in the early stages of insufficiency. Retinal artery pressures as measured with the Baillert ophthalmodynanometer[25] may be useful in carotid artery occlusion but have less value when that artery is partially stenosed.

The present study pursues the investigation of the tilt table electroencephalogram as a potential aid in making an early diagnosis of carotid or basilar artery insufficiency. Results obtained upon a group of such patients is evaluated by comparison with two groups of controls, one group matched for age and sex with the insufficiency group and the other made up of young male adults.

MATERIAL

The principal group (group 1) consisted of those who fulfilled the clinical criteria for basilar and carotid insufficiency. Those whose symptoms were recurrent hemiparesis, hemianesthesia, amblyopia, or aphasia, with or without a palpable decrease in the carotid pulsations in the neck, were classified as intermittent carotid syndromes for purposes of this study. There were 12 such cases ranging in age between 38 and 78 years, average 62. Fourteen subjects had been diagnosed tentatively as cases of basilar artery insufficiency on the basis of multiple episodes of diplopia, vertigo, nausea, vomiting, perioral numbness, cerebellar deficit, hemi- or quadriparesis, and so on. These were 54 to 84 years old, average 61. A 42-year-old female with a foramen magnum meningioma was included with this group because of the symptoms of insufficiency she presented and the information of value she contributed to the study. She will be discussed separately later.

Group 2 was a composite one made up of 26 controls matched for age and sex. These were chosen for absence of symptoms directly attributable to cerebrovascular disease. Seven had a history of other neurologic disorder. There were also two cases of symptomatic orthostatic hypotension of unknown etiology and two of hematologic disease. The latter four cases were selected for specific contributions they might make to the control aspects of the study.

Group 3 comprised 26 students whose average age was 23 years. They had no personal or family history of neurologic or cardiovascular disease.

The authors took the histories personally and also did complete neurologic examinations upon all subjects of groups 1 and 2. Routine skull films were taken upon all subjects in group 1. These were reviewed for calcification in the carotid siphon or in the common carotid at the bifurcation. One angiogram was available.

The tilt table rotated about a central axis, permitting a rapid tilt to 80°. In a moment it could be fixed securely at any angle. Tilting was manual at a speed designated in terms of degrees of tilt within an interval of seconds as measured by a stop watch. A guard protected the subject during tilt. The electroencephalograph input box was fixed to the tilt table and the procedure was carried out in a room shielded for sound and for electrical interference.

The subject lay upon the table (0° horizontal), with feet securely wedged to prevent slipping during the procedure. The method was described briefly to avoid any undue alarm which might change blood pressure or pulse rate. Resting blood pressure and pulse rate values were obtained. Needle electrodes were inserted subcutaneously into frontal, vertex, midtemporal, and occipital regions of the scalp upon each side. Recordings were bipolar. For pulse rate separate lead was taken from the precordium. The lead wires for the electroencephalograph electrodes were fastened to the table edge to reduce sway artifact. A

resting electroencephalogram was recorded and then the table was rotated through an arc of 40 to 50° in 10 to 12 seconds, the table remaining in that position for one or two minutes. If no electroencephalographic change occurred, the second tilt was carried to 75 to 80° over a 5 to 7 second period. This tilt was repeated two to three times before the results were tabulated as negative. Thereafter the subject was given a 15 to 20 minute rest before commencing carotid compression.

The carotid compressions were unilateral, of brief duration, and designed first to uncover any undue sensitivity to this procedure. Throughout most of the group 1 tests the initial compressions were undertaken at 45°. Otherwise (a few subjects of group 1 and all of group 2), the initial compressions were done in the horizontal position. If positive, further compressions were not undertaken. In all other subjects, carotid compression was applied for 20 to 30 seconds after a 75° tilt. Blood pressure was checked before and during carotid compression and any change was noted. Between compression of left and right carotids the subject was returned to the horizontal position for a brief rest. During compression the appearance of marked cardiac slowing or of any considerable degree of electroencephalographic abnormality was the signal for immediate release of pressure.

Group 3 subjects were handled identically with those of group 2.

RESULTS

Comparison of resting electroencephalograms showed a nearly equal incidence of disordered tracings in groups 1 (vascular insufficiency) and 2 (age and sex matched controls), 15 occurring in each group of 27 and 26, respectively. However, there were five focal records in the vascular insufficiency group, as compared with two among the matched controls. This abnormality is not unusual. Silverman and co-workers[26] earlier reported the occurrence of focal tracings in elderly functioning individuals who had had no preceding symptoms. The nonfocal disordered tracings were either slow, fast, or mixed fast and slow in character.

Tilt Alone

Between the group 1 (vascular insufficiency) subjects and their age and sex matched controls, there was little difference in blood pressure drop during tilt (over-all average 19-22/0-2) with the exception of the control subgroup of miscellaneous neurologic deficit subjects referred to previously. These showed the marked average blood pressure drop of 40/4. The group 3 young controls had an average drop of 6/0. None of the subjects showed a marked pulse rate change during tilt alone.

No electroencephalographic changes occurred in the group 2 controls upon tilt to 75°. Among the carotid insufficiency subjects of group 1, 11 of 12 also had negative tilts and the remaining one showed only an accentuation of a slow focus which had already been detected upon the side of the deficient carotid artery. Similarly, 13 of 14 basilar insufficiency subjects had negative tracings during tilt (table 1). The one exception developed a unilateral posterior triangle focus of theta frequency during tilt. Another subject (foramen magnum meningioma) showed bilaterally synchronous posterior delta frequency during the tilt, the appearance of which was associated with clinical signs of basilar insufficiency (figure 1). This case had particular importance because the neurosurgeon had visualized a constricting ring of tumor tissue encircling the left vertebral artery, and the right artery was so far displaced into the mass of tumor that its constriction also seemed probable. This sub-

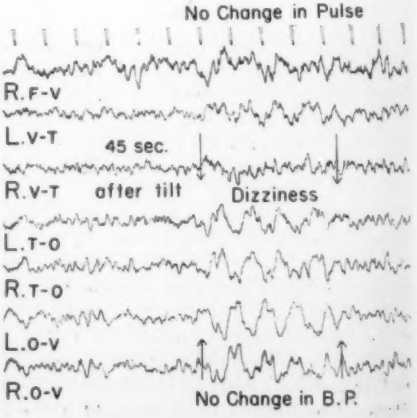

FIG. 1. Vertigo was described by patient as dizziness. This was associated with a spontaneous rotatory nystagmus during tilt.

ject developed the aggregate of her basilar insufficiency symptoms every time she sat upright in bed. The coincident electroencephalographic abnormality appeared with no change in blood pressure or pulse rate, showing conclusively that systemic vascular changes are not necessary to precipitate the insufficiency syndrome.

Application of Carotid Pressure

The more stressful procedure of unilateral carotid compression was carried out upon ten group 1 subjects with carotid insufficiency. Five of the ten (50 per cent) gave positive electroencephalographic results. In 11 subjects suspected of basilar insufficiency (excluding the meningioma), six (54 per cent) also gave positive results. In the age-sex matched controls, ten of 22 (45 per cent) showed positive results. The above include two subjects with carotid insufficiency, two with basilar insufficiency, and one group 2 control. These were not subjected to compression during tilt (table 2) because significant abnormalities appeared during compression in the horizontal position. Table 3 shows the incidence of electroencephalographic abnormal-

TABLE 1

		Number Subjects	*Average Age*	*Average BP (Resting)*	*Average BP Fall (Tilt)*	*Positive EEG With Tilt*
Group 1	Basilar insufficiency	14	61	163/92	22/0	1 (of 14)
	Carotid insufficiency	12	62	135/81	17/0	1 (of 12)
Group 2	Age-sex matched controls	26	66	132/78	22/2	0 (of 26)
Group 3	Young adult controls	26	23	122/74	6/0	0 (of 26)

BP = Blood Pressure

TABLE 2

		Number Subjects	*Positive EEG Carotid Pressure Without Tilt*	*Excessive PR Drop (>12) in "Positive" Subjects C.Pr. Without Tilt*
Group 1	Basilar insufficiency	11	2 diffuse (11)	2 (of 2)
	Carotid insufficiency	10	2 focal (10)	2 (of 2)
Group 2	Age-sex matched controls	22	1 focal (22)	1 (of 1)
Group 3	Young adult controls	26	0 (26)	0

C.Pr. = Carotid Pressure

TABLE 3

		Number Subjects	*Positive EEG Carotid Pr. With Tilt*	*Excessive PR Drop (>12) in Positive Subjects C.Pr. With Tilt*	*Excessive PR Drop (>12) in Negative Subjects C.Pr. With Tilt*
Group 1	Basilar insufficiency	11	4–3 F, 1 D (11)	1 (4)	1 (5)
	Carotid insufficiency	10	3 D (10)	1 (3)	2 (5)
Group 2	Age-sex matched controls	22	9–7 F, 2 D (22)	6 (9)	2 (12)
Group 3	Young adult controls	26	0 (26)	0 (0)	0 (26)

D = EEG, Diffuse Abnormality
F = EEG, Focal Abnormality

ities which developed upon carotid compression and tilt.

Several group 1 subjects showing electroencephalographic changes necessitate a more detailed report. One subject with presumptive right carotid insufficiency showed lateralized electroencephalographic changes upon either right or left carotid compression in the horizontal position, pulse rate falling to 12 per second on the right and 24 per second on the left. Another subject had a history of intermittent left hemiparesis (sometimes precipitated by head turning) and absent right carotid pulsation. Bifrontal and left central (delta) slowing developed with left carotid compression in the horizontal position (pulse rate drop from 78 to 60). This was associated with the subjective experience of jerking in the left arm. No electroencephalographic change occurred upon right carotid compression, although pulse rate dropped from 72 to 48 and blood pressure, 20/8. The right common carotid artery was later explored at another hospital and a thrombus found to occlude it which extended into both internal and external branches. After excision of the occluded segment, the subject no longer developed neurologic deficit upon rotation of the head. Evidently, head movement no longer activated a cardioinhibitory response.

Three other carotid insufficiency subjects of group 1 showed no electroencephalographic change with tilt plus compression of the insufficient artery, one of these having a marked pulse rate drop, the others none. By contrast, compression during tilt of the "good" carotid artery caused marked generalized electroencephalographic slowing, associated with syncope in two of the subjects and with dizziness in one. These findings suggested that the chief carotid supply to the circle of Willis (and through it to both hemispheres) occurred by way of the "good" vessel in these cases.

Two subjects with presumptive basilar insufficiency developed electroencephalographic abnormalities with carotid compression in the horizontal position. On left carotid pressure one subject showed generalized slowing of the electroencephalogram, the greatest abnormality occurring in the posterior lead combinations (pulse rate drop from 84 to 60; blood pressure drop 78/30). This result implied that the main supply to the circle of Willis was from the left carotid artery. Systemic vasodepressor and cardioinhibitory effects could have contributed largely to the blood pressure drop which occurred. The other subject also developed generalized electroencephalographic slowing with a right adversive seizure following left carotid compression (pulse rate drop from 84 to 50). Our explanation is the same. These two cases also emphasize the care which needs be taken in conducting carotid compression trials to establish the existence of a vascular insufficiency status.

Three of four subjects classified clinically as basilar insufficiency (group 1) developed asymmetric slowing at the posterior leads, while the fourth showed generalized slowing upon tilt and unilateral compression. In one subject the electroencephalographic findings were related to the complaint of numbness of the entire body. Two hemiparetic subjects with recent onset of symptoms suggestive of basilar insufficiency were coupled with electroencephalographic findings suggestive of carotid insufficiency. However, for purposes of this study these subjects were classified as negative members of the basilar insufficiency group.

In the group 2 age-sex matched controls one subject showed lateralized slowing upon compression of the corresponding vessel in the horizontal position. There was no blood pressure change in this case and a moderate pulse rate drop (right 132 to 96; left 138 to 132). Another of these subjects developed asystole upon carotid pressure at 75° tilt. This lasted five to eight seconds with compression of either carotid; however, no electroencephalographic change occurred with the asystole, illustrating perhaps the marked cerebral reserve which can exist in some asymptomatic subjects of this age.

Carotid compression during 75° tilt done upon group 3 (young) controls was entirely negative.

Summarizing, in 11 of 21 subjects with a diagnosis of carotid or basilar insufficiency, abnormal electroencephalographic findings appeared as a result of carotid compression. Abnormalities developed in seven of these only upon 75° tilt; they occurred in four subjects even in the horizontal position (table 3). This compares with ten positive results in 22 among

the age-sex matched controls of group 2. With one exception, none of the group 2 controls developed changes unless both tilt and compression were done. For the most part the electroencephalographic changes in group 2 subjects were signified by the appearance of slow activity of theta or delta frequency. This happened more often in frontal and temporal leads, less often diffusely.

Review of Skull Plates

Available roentgenograms of subjects with insufficiency syndromes were also reviewed. Of ten such cases with carotid insufficiency, three were negative, one having had a negative angiogram. Three others showed calcification of the siphon and one calcification at the bifurcation, all on the expected side. In another subject who had an innominate artery aneurysm the lateralization was indeterminate. On the other hand, two subjects showed calcification of either siphon or bifurcation on the non-suspected side. Of 14 subjects with basilar insufficiency, five had calcification in the carotid system, localizing either to the siphon or to the region of the bifurcation. Thus, in this small group there was little correlation between degree or side of electroencephalographic abnormality and roentgen findings.

DISCUSSION

With two exceptions, subjects diagnosed as having basilar or carotid insufficiencies (group 1) and all of the group 2 controls had no electroencephalographic changes upon rapid tilt alone (75° for five to seven seconds). Such a tilt occasioned an insignificant pulse rate change and an average blood pressure drop of only 22/0 (basilar insufficiency) and 17/0 (carotid insufficiency), as compared with 22/2 for group 2 age-sex matched controls (table 1). Only the subject having a basilar insufficiency syndrome resulting from tumor constriction of the vertebral vessels developed unequivocal electroencephalographic changes upon rapid tilt. In that case the tilt also produced symptoms of basilar insufficiency, but no alteration of blood pressure or pulse rate. Thus, from this part of the series it could be concluded that rapid tilt alone is not a sufficiently stressful procedure to be of practical aid in the early diagnosis of basilar or carotid insufficiency. It is perhaps interesting that Vander Eecken and Adams[13] also were unable to produce electroencephalographic changes by tilt in one patient with a history of vascular insufficiency.

In our series the blood pressure drop with sudden change in position from the horizontal to 75° increased significantly in older subjects. The drop was principally a systolic one (17 to 22), diastolic pressure rising as often as falling, as in the younger control group. Thus, maintenance of diastolic pressure and a relatively small systolic drop could explain the absence of electroencephalographic change in our group 1 subjects during tilt if this were the only determining factor. Of related interest is Millikan and Seikert's[21] observation that neither pulse rate nor blood pressure changed in several subjects when recorded prior to and during episodes of the typical neurologic deficit. As these authors remarked, there are probably a number of variables which interact to determine the adequacy of the cerebrovascular circulation in individual subjects, including anomalous anastamoses between vessels, degree and extent of atherosclerotic impairment in the cerebral collateral circulation, local and systemic blood pressure, cardiac disease, blood viscosity, and the susceptivity of the blood to clotting.

With respect to maintained effectiveness of cerebral circulatory reserve during tilt, Stevens and Fazekas[27] produced marked and rapid blood pressure drop by tilt following the injection of ganglionic blocking agents, without the occurrence of electroencephalographic changes. In our group 2 controls there were two subjects with pertinent findings. One of these had orthostatic hypotension with syncope (blood pressure drop on tilt 42/22) and another hematologic disease (hematocrit 30 per cent, blood pressure drop on tilt 36/8). Neither showed any electroencephalographic changes with tilt.

Since tilt alone did not produce positive results in our study, the evaluation of the effect of carotid compression with tilt takes on added importance. Compression of the carotid during tilt may occasion electroencephalographic changes and associated neurologic symptomatology in subjects suspect of vascular insufficiency, but this may also develop among age-sex matched controls. Direct compression of a

carotid artery with reduction in the flow of blood it carries can produce marked electroencephalographic changes, depending upon the patency of collateral vessels, including the companion carotid. Besides compression, other factors may also play a role. A sensitive carotid sinus, when stimulated during compression, may produce a cardioinhibitor or vasodepressor effect,[28] contributing to a decrease in total blood flow to the cerebrum. This alone could account for 1) the electroencephalographic effects obtained by compression of an apparently occluded vessel and 2) some of the electroencephalographic abnormalities obtained by carotid compression in subjects with basilar insufficiency symptoms. It should be noted that the majority of those vascular insufficiency and age-sex matched control cases which developed no electroencephalographic changes upon tilt plus compression had a relatively stable carotid sinus mechanism, as did all of the group 3 young control subjects.

It was also evident that subjects who developed abnormalities in their electroencephalograms upon compression without tilt showed a marked pulse rate drop. Under this circumstance, four of 21 insufficiency subjects (19 per cent) and one of 22 (5 per cent) in the age-sex matched control group developed diffuse or focal electroencephalographic abnormalities (table 2).

Three subjects with carotid insufficiency who developed syncope or severe dizziness with tilt and compression did so as a response to compression of the "good" carotid and without significant pulse rate drop (one exception). Presumably this carotid carried the major blood supply to both hemispheres. Gurdjian and Webster[29] reported similar findings in suspected carotid occlusion when checking the effect of digital compression of the good vessel by appearance of symptoms alone.

Excluding those subjects with sensitive sinus mechanisms who even developed electroencephalographic changes on compression with the table horizontal, only seven subjects in the entire group 1 had positive electroencephalographic findings activated like those previously described by Meyer and co-workers.[19] In these subjects a marked reduction in cardiac rate and pressure was not a primary factor, as it was in a majority of nine matched controls (group 2) who developed diffuse delta upon compression (table 3).

Even minimizing the complications occasioned by carotid sinus sensitivity (important for our group 2 controls), the over-all variability in the electroencephalographic findings with tilt and compression does not suggest the utility of the procedure for obtaining evidence for the existence of an insufficiency state. Although supporting the previous study in significant detail, our results differ in general from those of Meyer and co-workers,[9] who obtained a high incidence of positive results with tilt alone. With the clinical diagnostic impression as the chief criterion for selection of subjects, it is believed unwise to inflate the significance of the general differences which exist, for in a small series chance always mitigates seriously against close conformity in results. The discrepancies do indicate the need for a much larger series obtained under uniform conditions and from a variety of sources. The methods introduced by Meyer and associates[24] could have individual significance in comparing the physiologic consequence of stress before and after anticoagulant or other therapy used to modify the insufficiency state.

Sixty per cent of subjects in the carotid insufficiency group had calcification in one or the other carotid artery, either at the bifurcation or the siphon and more frequently upon the side of the insufficiency. In the basilar group 36 per cent showed a similar distribution of carotid calcification. Fisher and Miller[4] noted that there may be marked calcification at the carotid sinus on one side and relatively little change upon the other. Other authors[30] have found atherosclerotic changes in the carotid sinus in 50 of 55 cases unselected for cerebrovascular disease. Hultquist[14] (quoted by Fisher and Miller[4]) noted that atherosclerotic placques occur at the siphon about one-third as often as in the region of the sinus. In our subjects there was no correlation between sensitivity of a carotid sinus and calcification visible at the bifurcation of the carotid.

SUMMARY

1. In subjects with carotid or basilar insufficiency, rapid tilt alone did not produce electroencephalographic changes, due presumably to maintenance of the pre-tilt diastolic pressure

during tilt. Thus, our results do not indicate that tilt alone provides a useful confirmatory test for the vascular insufficiency syndromes. The results also suggest that for most patients a drop in systemic blood pressure is not the sole factor precipitating insufficiency symptoms.

2. There was a marked reduction in pulse rate in all subjects of both insufficiency and age-sex matched control groups who showed electroencephalographic changes upon unilateral compression without tilt, with the inference that a secondary decrease in unit blood flow to the brain had brought about relative focal or generalized ischemia.

3. Seven of 21 subjects in this series (three carotid, four basilar) and nine of 22 of the age-sex matched controls (excluding those positive findings without tilt) showed electroencephalographic changes upon tilt and unilateral carotid compression. Thus, like tilt alone, carotid compression plus tilt did not aid in differentiating subjects with a history of vascular insufficiency from matched controls.

4. The results obtained emphasize the many variables involved in the interpretation of data relating to the vascular insufficiency syndrome and the need for an extensive series as a prelude to final appraisal. Factors which occasion variability include selection of material, mechanics of the test, irritability of the carotid sinus, and adequacy of homeostatic mechanisms available for compensatory purposes.

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Effects of bilateral cerebral infarction on respiratory center sensitivity

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ALTHOUGH the control of breathing is primarily a function of the medullary respiratory center, this basic regulatory mechanism is often modified by higher cerebral levels and by alterations in blood carbon dioxide. Lesions of the cerebral hemisphere and brain stem are known to be associated with various respiratory changes, including periodic breathing, Cheyne-Stokes respiration, and pulmonary hypoventilation or hyperventilation.[1–3] Apart from observations on these respiratory changes, there are few methods of determining whether the respiratory center has been affected in patients with brain damage.

One such method may be the measurement of the response to inhalation of a small concentration of carbon dioxide. This technic has been employed in patients with various pulmonary disorders, as well as in physiologic studies of respiratory function.[4,5] However, there is little information about the responsiveness of the respiratory center to carbon dioxide inhalation in patients with lesions of the central nervous system.

The present report summarizes our findings on the effects of this carbon dioxide stimulus on the neural respiratory mechanisms in patients with bilateral cerebral infarction. The changes in arterial *p*H, blood gases, and pulmonary ventilation in this group of subjects were also studied and compared with controls.

METHODS

Respiratory functions were studied in eight male patients with severe chronic brain damage caused by bilateral cerebral infarction. Their ages ranged from 60 to 72 years, with a mean of 65 years. In addition to motor and sensory involvement, they showed emotional instability, speech and swallowing defects, increased jaw jerk, and bilateral extensor plantar reflexes (table 1). There was no clinical evidence of infarction of the brain stem. Only one patient was comatose; the remainder showed only slight decrease in awareness, manifested by disorientation, confusion, or slow responses to simple questions and commands. Clinical evidence of cerebral vascular disease had been present approximately one to two years, the last vascular episode appearing one to three weeks prior to the study. Electroencephalograms showed diffuse bilateral abnormalities in six of the eight patients. Periodic respiration had been observed in seven of the eight patients sometime during their hospital stay, but only one had Cheyne-Stokes respiration during the actual study. None showed clinical evidence of congestive heart failure. Postmortem examination in four patients showed bilateral cerebral infarction in various areas of the cortex and in the internal capsule. There were no gross lesions demonstrable in the brain stem.

Comparison studies were done in two additional groups of patients of the same ages. One group consisted of seven patients with a single cerebral infarction and unilateral hemisensory or motor defects. The other group comprised nine patients aged 50 years or over, who were convalescing from chronic ill-

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TABLE 1
CLINICAL AND NEUROLOGIC FINDINGS IN BILATERAL CEREBRAL INFARCTION

Patient	Hemiparesis R	Hemiparesis L	Extensor Plantar R	Extensor Plantar L	Jaw Jerk	Dysarthria and Dysphagia	Emotional Lability	Changes in Awareness	Cheyne-Stokes Resp.	Remarks
L. P.	+	0	+	0	+	+	+	+	+	Autopsy—Left cortical and bilateral basal ganglia infarcts
R. P.	0	+	+	+	+	+	0	+	+	Autopsy—Bilateral cortical infarcts
W. B.	+	0	0	0	+	+	+	+	+	Progressive dementia—1 year
C. C.	+	+	+	+	+	+	+	+	+	
S. P.	+	+	+	0	+	0	+	+	+	Autopsy—Bilateral cortical infarcts
J. H.	+	+	+	+	+	+	+	+	+	Recurrent cerebral ischemia
R. B.	+	+	+	+	0	+	+	+	+	
J. C.	+	+	+	0	0	+	0	Coma	0	Autopsy—Right cortical infarcts—left capsuel

nesses such as psychophysiologic headaches, peripheral neuropathy, and rheumatoid arthritis. All 16 subjects were alert and oriented, without evidence of pulmonary or diffuse brain disease. A third control group consisted of nine healthy males under the age of 30 years.

Initial samples of air and blood were collected from each subject while he was awake and supine for at least 15 minutes. The volume of expired air was measured during periods of three to four minutes and a blood sample was taken during this time over a 30- to 60-second period. Air samples were obtained in Douglas collecting bags connected to a face mask firmly attached about the subject's nose and mouth. Care was taken to avoid leakage about the mask. The dead space of the system was 60 cc. Arterial blood samples were taken in oiled heparinized syringes from an indwelling Cournand needle inserted into the brachial artery.

Following collection of the initial samples, the subjects were given a mixture of 5 per cent carbon dioxide, 21 per cent oxygen, and 74 per cent nitrogen instead of room air. Samples of blood and expired air were obtained at the end of five minutes of inhalation of this gas mixture. Longer periods of carbon dioxide inhalation were not carried out because the patients with brain damage often were unable to tolerate it. In five patients carbon dioxide inhalation had to be discontinued after two or three minutes because of marked subjective distress and hyperpnea.

The volume of expired air was measured and converted to standard temperature and pressure. Blood oxygen content and saturation were determined by the photometric method of Hickam and Frayser.[6] Blood carbon dioxide was determined by the method of Van Slyke and Neill.[7] The *p*H of whole blood was measured with a Cambridge model R *p*H meter with enclosed glass electrodes; measurements were corrected to 37° using Rosenthal's factor.[8] Plasma carbon dioxide content was calculated from the blood carbon dioxide content, *p*H, and hemoglobin, using the line chart of Van Slyke and Sendroy;[9] carbon dioxide tension was calculated from this value, using the Henderson-Hasselbach equation with a pK of 6.11. The use of this constant produces pCO_2 values slightly higher than those generally reported for normal subjects. All blood determinations were done in duplicate.

RESULTS

The values obtained at rest and during carbon dioxide inhalation in the control subjects and in patients with cerebral infarction

TABLE 2

CHANGES IN ARTERIAL BLOOD GASES AND PULMONARY VENTILATION AFTER 5 MINUTES INHALATION OF 5% CO_2

Subject	Age	Blood O_2 % Sat. C	Blood O_2 % Sat. E	Blood pCO_2 mm. Hg C	Blood pCO_2 mm. Hg E	Blood pH C	Blood pH E	Total Vent. L/min. C	Total Vent. L/min. E	Resp. per min. C	Resp. per min. E	CO_2 Sensitivity L/min./mm. Hg pCO_2
YOUNG CONTROL SUBJECTS												
B. S.	17	93	97	41.2	51.2	7.406	7.338	8.5	30.5	16	25	2.20
J. P.	21	98	98	41.8	56.5	7.387	7.299	8.3	16.1	13	13	0.53
J. M.	24	98	98	47.5	55.9	7.375	7.319	6.7	17.8	16	18	1.32
N. G.	24	95	94	47.6	54.9	7.377	7.320	7.5	17.2	19	17	1.33
G. T.	24	97	97	45.9	60.1	7.366	7.279	6.7	25.8	9	13	1.35
L. K.	23	96	96	44.3	59.9	7.386	7.292	6.9	15.3	13	12	0.54
B. C.	21	96	98	45.9	56.2	7.404	7.338	5.6	18.4	11	17	1.24
J. C.	22	95	97	45.5	61.2	7.374	7.282	8.3	28.8	17	19	1.31
J. J.	21	96	98	47.0	61.1	7.370	7.280	7.7	24.0	16	17	1.16
Mean	23	96	97	45.2	57.4	7.383	7.305	7.4	21.5	14	17	1.22
OLD AGE CONTROL SUBJECTS												
W. C.	63	95	96	48.9	59.7	7.341	7.278	8.2	17.8	17	18	0.89
H. L.	50	94	98	53.9	58.5	7.334	7.310	4.4	10.4	16	19	1.30
W. B.	58	94	96	45.0	54.0	7.397	7.337	6.0	12.3	14	16	0.70
A. A.	65	92	96	40.0	48.8	7.423	7.356	8.8	16.6	19	17	0.89
A. A.	68	95	97	45.5	53.5	7.363	7.303	11.1	29.0	19	22	2.24
R. A.‡	67	95	97	44.2	58.2	7.384	7.288	8.8	31.3	20	24	1.61
H. S.	59	89	95	45.2	62.2	7.373	7.261	10.4	26.5	20	21	0.95
N. W.	50	98	100	41.3	54.4	7.370	7.280	6.7	25.5	16	18	1.44
J. L.	59	97	98	42.6	58.4	7.439	7.326	6.4	18.0	18	22	0.73
Mean	60	94	97	45.2	56.4	7.380	7.305	7.9	20.8	18	20	1.19
UNILATERAL CEREBRAL INFARCTION												
A. O.	51	92	98	44.5	52.4	7.366	7.310	11.9	33.9	20	24	2.78
J. C.	36	93	96	36.9	47.6	7.396	7.321	8.7	18.7	14	17	0.93
R. B.	52	96	97	49.6	51.6	7.347	7.341	5.9	10.2	14	19	2.15
F. C.	54	95	98	53.6	55.2	7.366	7.363	6.5	11.3	35	28	3.00
A. P.‡	67	96	100	43.1	48.7	7.375	7.299	7.7	27.9	14	22	3.61
R. D.	64	91	97	37.8	53.9	7.368	7.255	9.6	36.2	23	28	1.65
S. K.	59	96	96	39.8	49.8	7.396	7.321	8.1	35.3	8	19	2.72
Mean	55	94	97	43.6	51.3	7.373	7.316	8.3	24.8	18	22	2.41*
BILATERAL CEREBRAL INFARCTION												
L. P.	61	94	97	38.2	47.6	7.395	7.316	7.9	38.2	22	33	3.22
W. B.	61	93	96	49.3	54.8	7.364	7.326	7.8	20.6	17	24	2.33
C. C.‡	68	95	97	39.0	47.5	7.443	7.376	7.5	28.8	12	21	2.51
S. P.	61	96	96	39.4	47.2	7.417	7.348	8.1	25.1	29	32	2.19
R. P.‡	60	94	96	36.0	45.1	7.423	7.354	11.7	34.7	22	27	2.53
J. H.‡	69	91	95	41.6	46.2	7.418	7.381	7.7	24.7	21	32	3.70
R. B.	68	96	99	46.0	49.1	7.394	7.383	8.5	24.3	18	22	5.10
J. C.‡	72	91	94	38.0	49.4	7.444	7.359	6.0	25.3	22	30	1.69
Mean	65	94	97	40.9†	48.4	7.412†	7.355	8.2	27.7	20	28*	2.91*

C—Resting values while breathing room air.
E—Values after inhalation CO_2.
*—Statistically significant differences from young and old control subjects ($p < .01$).
†—Statistically significant differences from young or combined group of control subjects ($p < .05$).
‡—Carbon dioxide inhalation discontinued in less than three minutes.

are shown in table 2. Patients with bilateral cerebral infarction had a resting respiratory rate of 20 per minute, whereas the young and old age control subjects showed lower values of 14 ($p < .02$) and 18 per minute, respectively. Patients with unilateral cerebral infarction showed a wider range in their resting respiratory rate, with a mean of 18 respirations per minute. Despite these differences in respiratory rates, the resting minute volumes were essentially the same in all four groups of subjects, the values ranging from

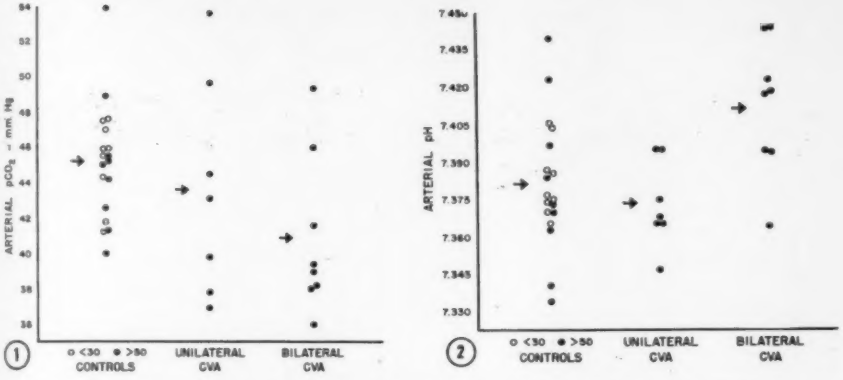

FIG. 1. Values for arterial carbon dioxide tension in each of the patients in this study. The arrows indicate the mean value in each group. The open circles in the control group represent young volunteer subjects under 30 years of age; the closed dots represent convalescing patients over 50 years of age.

FIG. 2. Values for arterial pH in each of the patients in this study. The arrows indicate the mean value in each group. The open circles in the control group represent young volunteer subjects under 30 years of age; the closed dots represent convalescing patients over 50 years of age.

7.4 in the young subjects to approximately 8.2 liters per minute in all older individuals.

The mean resting arterial carbon dioxide tension in patients with bilateral cerebral infarction was 40.9 mm. Hg, a value significantly less than that of 45.2 in the young control subjects ($p < .05$). The old age control group, however, showed a wider range of pCO_2 values at rest. They had a mean of 45.2 mm. Hg, which was not significantly different from that of the patients with cerebral infarction ($p < .1$). Three of the seven patients with unilateral cerebral infarction had low pCO_2 values comparable to those with bilateral lesions, the mean for the group being 43.6 mm. Hg (figure 1).

Patients with bilateral cerebral infarction had a mean arterial pH of 7.41 (figure 2), which was significantly greater than that of 7.38 observed in the control subjects ($p < .05$) and that of 7.37 in the patients with unilateral infarction ($p < .01$). The resting oxygen saturation varied between 93 and 96 per cent without any significant difference among the groups.

The ventilatory response to carbon dioxide inhalation in these groups differed significantly, as illustrated by the comparison of two patients in figure 3. In those with bilateral cerebral infarction, carbon dioxide inhalation produced a prompt and marked increase in respiratory rate from 20 to 28 per minute. This was significantly greater than the increase of two to four respirations per minute observed in the control subjects ($p < .01$). The relationship of the increase in minute ventilation to the change in arterial pCO_2 in patients with bilateral brain damage and in the older control subjects is shown in figure 4. It is apparent that patients with bilateral infarction responded to carbon dioxide inhalation with a greater increase in ventilation than the control group. The mean ventilatory response to the carbon dioxide stimulus in patients with bilateral cerebral infarction was 2.91 liters of expired air per minute per mm. Hg pCO_2. This is significantly greater than the mean ventilatory response of 1.2 liters per minute per mm. Hg found in either group of control subjects ($p < .01$). The patients with unilateral infarction also exhibited a significantly greater response than the control subjects to carbon dioxide inhalation, with an intermediate value of 2.4 liters per minute per mm. Hg pCO_2 ($p < .01$).

Arterial blood gas determinations were repeated over a period of three to five months in four of the eight patients with bilateral cerebral infarction. The values remained approximately the same during this period of

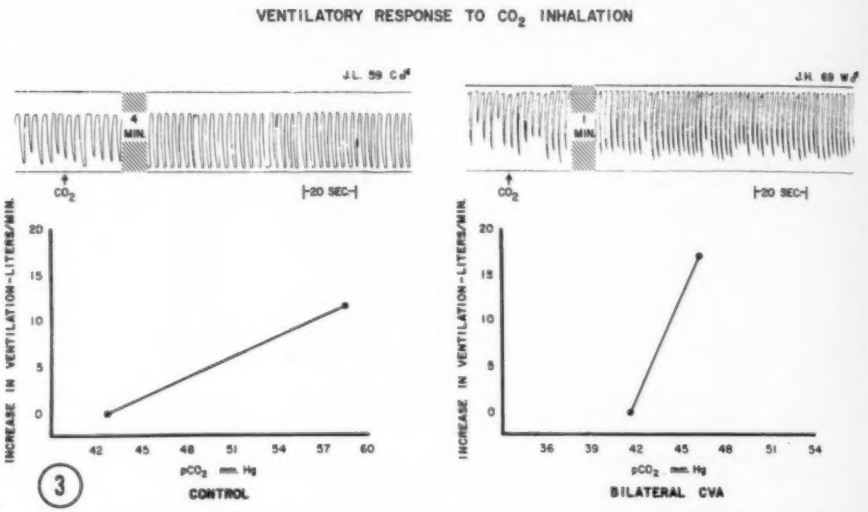

FIG. 3. Representative respiratory responses to carbon dioxide inhalation in a patient with bilateral cerebral infarction and in an old age control subject. The pneumograms in the upper portion of the chart show marked differences in respiratory rates following carbon dioxide inhalation.

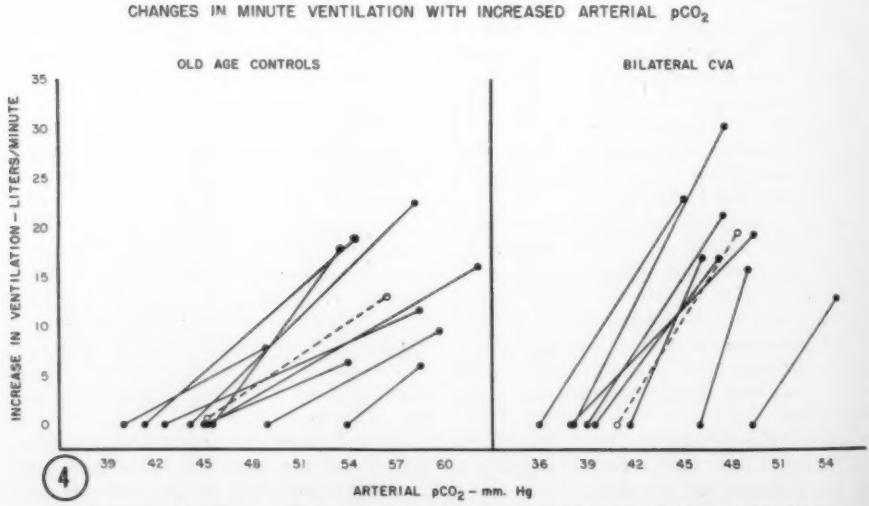

FIG. 4. Changes in minute ventilation and arterial pCO_2 during carbon dioxide inhalation in the old age control subjects and in patients with bilateral cerebral infarction. The dotted lines indicate the mean of each group.

time. The respiratory sensitivity also showed no change in the two patients in whom this study was repeated.

DISCUSSION

These results indicate that lesions of the cerebral cortex are associated with an increase in the sensitivity of the respiratory center to carbon dioxide stimulus. The areas of the brain in man known to alter respiration are the lower precentral area, the posterior orbital surface of the frontal lobe, and the anterior limbic system, including the tip of the temporal lobe and hippocampus.[10] Of these, only the posterior orbital area in the monkey has been found to alter the regulation of blood gases.[11] Destruction of the tracts descending from this area allows the animal to maintain a prolonged period of hyperpnea in low pressure chambers, presumably because they were able to tolerate lower levels of carbon dioxide tension than control animals. In this respect, experimental cerebral damage produces a situation analogous to that observed in our patients with brain lesions.

The explanation for the hypocapnia observed in our patients with bilateral cerebral infarction is not clear. There is some evidence to suggest that normal old age subjects have a a low arterial carbon dioxide tension, but the differences from healthy young adults were not found to be significant.[12] Only one of our patients (R.P.) showed an increased ventilation at the time the resting blood samples were drawn; the remaining cases showed no evidence of hyperventilation. It seems possible that brain damage may initially produce a transient period of hyperventilation lasting perhaps hours or days,[13] a response similar to that observed in subjects returning to sea level from high altitudes or in patients following hyperventilation in artificial respirators.[14] This may alter the sensitivity of the respiratory center to carbon dioxide, so that a reduced carbon dioxide tension is sufficient to maintain the same respiratory ventilation which previously required a greater stimulus. Thus, patients with brain damage may ultimately maintain a normal minute ventilation with a lower than normal level of arterial pCO_2. Studies in animals suggest that this change in the neural respiratory mechanism may be related to a reduction in the buffering capacity of brain tissue to carbon dioxide.[15]

The presence of Cheyne-Stokes respiration in seven of our eight patients with bilateral infarction was not surprising, since this form of periodic breathing had been reported in such patients more than 60 years ago by Hughlings Jackson. Recently, postmortem studies have shown that Cheyne-Stokes respiration is more likely to be associated with lesions of the cerebral hemispheres than with brain stem damage.[1] The role of the cerebral cortex in production of periodic breathing has been investigated by Hoff and Breckenridge,[16] who concluded that the higher cerebral centers exert a suppressor influence upon brain stem respiratory mechanisms. Elimination of the cortical influence allows the various periodic breathing patterns intrinsic in the brain stem to become apparent. A recent report indicates that patients with lesions of the brainstem also show changes in arterial blood gases and respiratory center sensitivity similar in some respects to our cases with bilateral cortical damage.[14] Both groups have hypocapnea, but those with brain stem lesions had obvious clinical hyperpnea.

Cheyne-Stokes respiration in itself cannot account for the increased respiratory center sensitivity or the lower carbon dioxide tensions observed in our patients. This form of periodic breathing is usually associated with increased arterial pCO_2 and reduction of respiratory sensitivity when occurring in sleep and in the obesity-cardiopulmonary syndromes.[17,18] On the other hand, Cheyne-Stokes respiration in congestive heart failure is more likely to be associated with a lower carbon dioxide tension, although considerable variability exists.[19]

Seven of our patients with bilateral cerebral infarction had a slight decrease in awareness, but only one was comatose. A retention of carbon dioxide in these individuals would be expected, similar to that seen in other states of decreased awareness such as sleep, narcolepsy, and hypersomnolence.[17,20] It is apparent, however, that the changes in respiratory function seen in physiologic states of altered consciousness (for example, sleep) are the converse of those noted in patients with loss of awareness due to brain damage.

The dramatic response of the respiratory center to carbon dioxide in our patients with bilateral infarction is comparable in some respects to other exaggerated responses, such as the emotional lability and hyperreflexia which are also seen in these patients. These heightened responses are interpreted as indicating neuronal "release" mechanisms. It is apparent from our data that cortical damage may produce a similar "release" of the respiratory center, permitting it to operate at lower controlling levels of carbon dioxide tension.

SUMMARY

The ventilatory response to carbon dioxide inhalation and the alterations in arterial blood gases were studied in eight patients with bilateral cerebral infarction and compared with control subjects. These patients showed evidence of hypocapnea at rest and an increased ventilatory response to carbon dioxide inhalation. This increase in sensitivity of the respiratory center to chemical stimulation may be due to the elimination of cortical suppressor influences. The response to carbon dioxide stimulus observed in our patients is another of the exaggerated responses seen in patients with bilateral cerebral infarction.

We are indebted to Mrs. Mary Pike and Miss Corinna Thomas for their valuable technical assistance.

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Implications of a five-year study of 700 basal ganglia operations

Irving S. Cooper, M.D., and Gonzalo J. Bravo, M.D.

IT IS THE PURPOSE of this report to summarize an intensive study of the effects of 700 globus pallidus and thalamic lesions in persons afflicted with parkinsonism and diverse involuntary movement disorders.

ANTERIOR CHOROIDAL ARTERY OCCLUSION

Selective anterior choroidal artery occlusion was performed in 55 patients between 1952 and 1955. Follow-up examination of these 55 cases of anterior choroidal artery occlusion periods ranging from two to five and one-half years following surgery has demonstrated that this operation provided the most complete and lasting relief of far advanced incapacitating rigidity, tremor, and deformity that had been reported anywhere in the literature up until that time.[1,2] Many of the patients who were completely relieved of tremor, rigidity, and deformity from the side of the body contralateral to surgery not only have remained relieved of these symptoms up to the present time, but they have also become ambulatory and independent in their daily life.

Conclusions which can be documented without question as a result of the follow-up studies in these 55 cases of anterior choroidal artery occlusion are as follows: 1) The effectiveness of anterior choroidal artery occlusion is due to infarction of more than a single small anatomic structure and probably involves a physiologic unit of two or more intracerebral structures, principally the mesial part of the globus pallidus and the ventrolateral region of the thalamus (figure 1). 2) Total relief of tremor, rigidity, incapacitation, and deformity is possible by neurosurgical means without inflicting any neurologic deficit upon the patient (figure 2). 3) Objective evidence of five-year cure of the parkinsonian *symptoms* of tremor, rigidity, and deformity has been achieved by anterior choroidal artery occlusion. 4) The dystonic deformities seen in some parkinsonian patients are not actually fixed deformities but represent forced postures which are reversible, even after many years' standing. 5) The so-called syndrome of the anterior choroidal artery is not invariable, and in many cases this vessel may be completely occluded without producing observable neurologic deficit. However, anatomic variations of the vessel, particularly the lack of collateral blood supply to the posterior limb of the internal capsule in the aged, would make routine employment of anterior choroidal artery occlusion unwise. 6) The unquestioned ability of this procedure to relieve tremor and rigidity without inflicting any neurologic deficit warranted further steps to develop neurosurgical technics which might be more universally applicable to a broader spectrum of the parkinsonian population.

CHEMOPALLIDECTOMY AND CHEMOTHALAMECTOMY

The technics of chemopallidectomy[3,4] and chemothalamectomy[5] combine roentgen-anatomic methods of lesion placement deep in the brain, with clinical physiologic confirmation of the results in a conscious, cooperative patient. As presently performed, the technic consists of the following basic steps. 1) Pneumoencephalography with 30 cc. of air in

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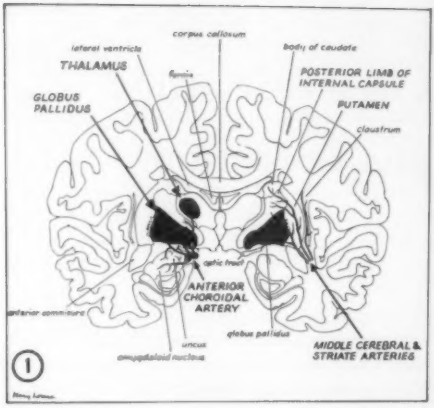

FIG. 1. A diagrammatic representation of the irrigation of a physiologic unit consisting of the mesial globus pallidus, posterior limb of the internal capsule, and ventrolateral region of the thalamus by the anterior choroidal artery.

FIG. 2. *A*. Photograph made from cinematographic record of a patient with far advanced parkinsonism. Note particularly the marked advanced deformity of the left hand and earlier deformity of the right hand. *B*. These are the same hands five years after right anterior choroidal artery occlusion and four years after left chemopallidectomy. Note the complete relief of the rigid dystonic deformity of the left hand persisting for five years after anterior choroidal artery occlusion. This case represents one of those among the group who now demonstrate five-year relief of tremor, rigidity, and deformity in this series.

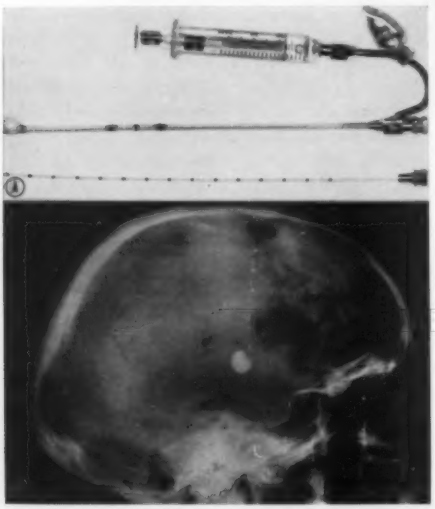

FIG. 3. *A*. Polyethylene cannula used for chemopallidectomy. Note that it has a double lumen. One of these leads to a small inflatable balloon at its tip. Inflation of this balloon within the globus pallidus or thalamus provides a physiologic test of the effects of a lesion in this region in the conscious cooperative patient. It also produces a cavity for subsequent injection of alcohol and Pantopaque which results in a circumscribed lesion. *B*. Roentgenogram made during operation demonstrating the balloon in place in the region of the globus pallidus after it has been inflated with 0.4 cc. of Hypaque.

order to visualize the anterior portion of the ventricular system, especially the foramen of Monro. 2) Introduction of a polyethylene brain cannula through a small skull trephine. This cannula is placed under roentgenographic control into the region of the globus pallidus or ventrolateral nucleus of the thalamus. 3) Distention of a small balloon at the tip of the cannula in order to provide a clinical physiologic test of the effects of a lesion in this region. In addition to providing such a physiologic test, the balloon produces a cavity in the desired region of the brain for subsequent injection of absolute alcohol and Pantopaque in order to produce a circumscribed and

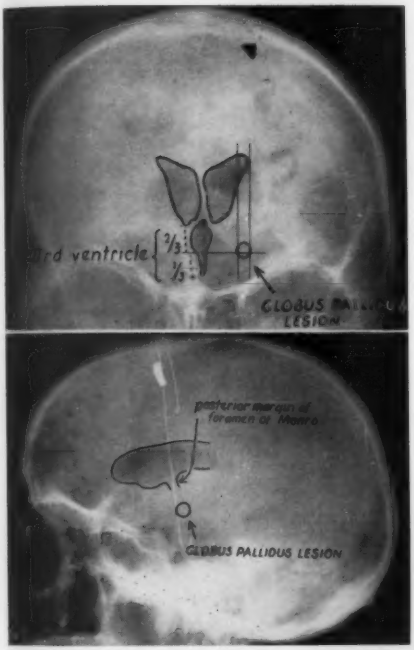

FIG. 4. Anteroposterior and lateral pneumoencephalograms demonstrating the roentgenographic landmarks of the globus pallidus lesion produced by chemopallidectomy.

localized permanent lesion (figure 3). 5) The cannula remains indwelling in the brain for several days following surgery so that the lesion may be enlarged if necessary in order to produce lasting relief of the contralateral hyperkinetic symptoms. The anatomic landmarks used in the production of these lesions are summarized in the accompanying illustrations (figures 4, 5, 6, and 7).

The production of a large lesion in the globus pallidus by the technic of chemopallidectomy proved to be a relatively simple procedure, with a small morbidity and mortality rate. Favorable results were obtained in 70 per cent of cases. However, although rigidity could be relieved in 80 per cent of such cases, tremor was relieved in only 60 per cent. In such cases the tremor responded favorably when a second lesion was placed on a plane approximately 10 mm. behind the original globus pallidus lesion or approximately 15 mm. behind the posterior margin of the foramen of Monro. Anatomic studies permitted us to identify the second area as a zone which included the pallidothalamic connections with the anteroventral portion of the thalamus. In some instances the second lesion is localized within the ventrolateral region of the thalamus itself.

In subsequent experience with several hundred cases, this latter lesion in the region of the ventrolateral nucleus of the thalamus proved so successful for cases that had been incompletely relieved of tremor by the pallidal lesion alone that it gradually became our practice to produce a thalamic lesion primarily in cases in which tremor was the presenting symptom. When this thalamic lesion is properly placed, virtually complete relief of tremor is obtained in 90 per cent of cases of patients.

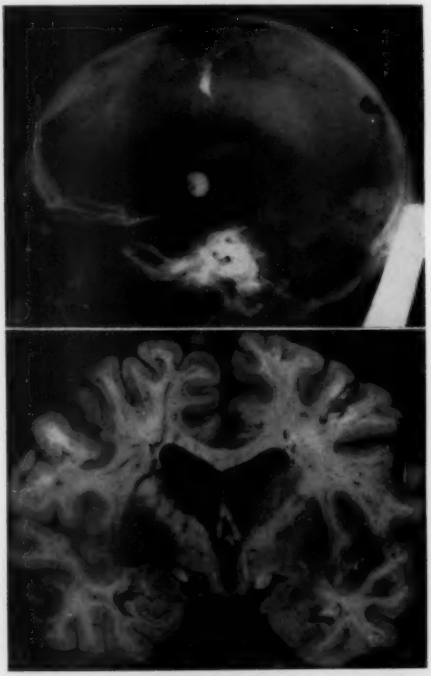

FIG. 5. *A*. Lateral roentgenogram made during performance of chemopallidectomy in a cadaver as part of a controlled anatomic experiment. *B*. Anatomic specimen from the operation represented in *A*. Note the globus pallidus lesion corresponding to the roentgenogram made during the operation.

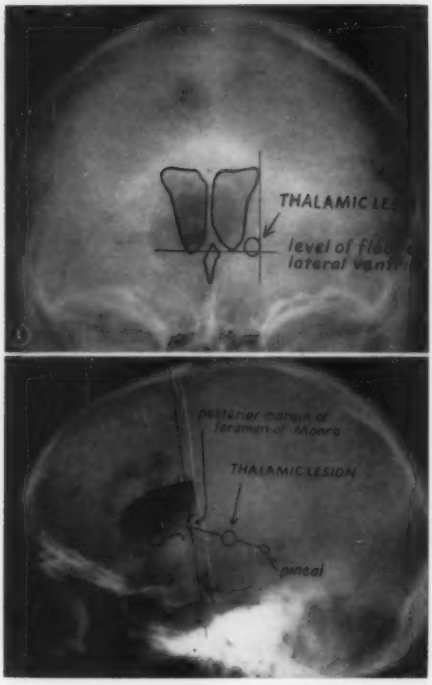

FIG. 6. Pneumoencephalographic landmarks of the thalamic lesions produced by chemothalamectomy.

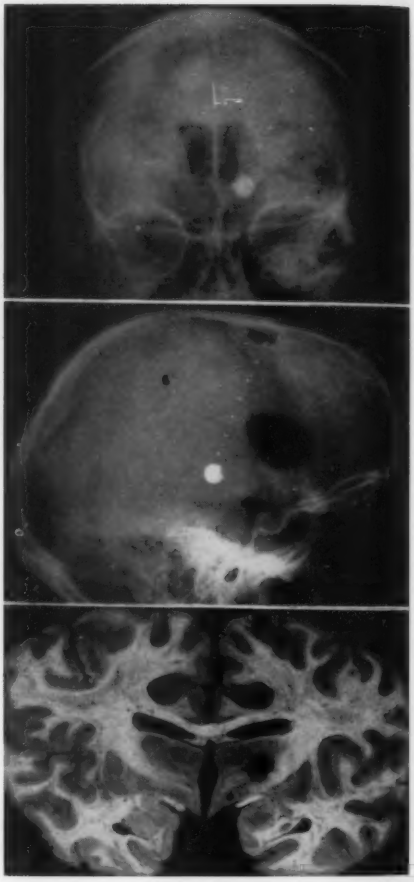

FIG. 7. *A*. Anteroposterior roentgenogram made during performance of chemothalamectomy in cadaver experiment. *B*. Lateral roentgenogram made during same cadaver experiment. *C*. Anatomic specimen representing the cadaver operation referred to in figures 7A and B. Note the circumscribed lateral thalamic lesion.

Moreover, this relief is complete and lasting. Results of these 700 operations, together with our analysis of the important contributions of others[6–10] lead us to conclude that two factors are responsible for the complete relief of tremor and rigidity in our cases, as opposed to the experience of some other investigators. These factors accounting for the complete relief of tremor are: 1) the production of relatively large circumscribed lesions and 2) the thalamic component of our lesions.

There is no question but that a lesion in the region of the ventrolateral nucleus of the thalamus has a more complete and absolute effect on contralateral resting tremor than does the pallidal lesion alone. Several irrefutable facts are now apparent. Tremor, rigidity, deformity, and incapacitation of parkinsonism can be relieved by properly placed lesions of the globus pallidus or thalamus or both, without the infliction of any motor, sensory, or intellectual deficit upon the patient. Furthermore, by the use of chemopallidectomy and thalamectomy, this can be accomplished consistently with reasonable safety, namely, a mortality rate of 2.4 per cent and hemiplegia rate of 3 per cent.

From a surgical standpoint one must perform the technic meticulously, with accuracy in placement of the cannula and persistence

in production of an adequately sized, properly developed basal ganglia lesion.

From a clinical standpoint proper selection of patients is essential. The principal contraindications to these operations at the present time are as follows: 1) organic mental deterioration; 2) psychosis; 3) pseudobulbar palsy; 4) a preponderance of vegetative and akinetic symptoms, as opposed to a preponderance of tremor or rigidity; 5) physiologic old age—although many cases have been operated successfully in the seventh and even the eighth decades of life, one must select patients in this age group who are physiologically well preserved, do not show organic mental deterioration, and have much more involvement of tremor and rigidity on one side of the body than on the other; and 6) general medical contraindications as, for example, severe hypertension.

NEUROLOGIC OBSERVATIONS

Many observations of interest have been made during the analysis of these cases. A five-year study of all cases from a clinical psychologic standpoint before and at various follow-up periods after operation has been carried out. In no case has a lesion which has been circumscribed in the mesial globus pallidus or the ventrolateral region of the thalamus produced any lasting intellectual or emotional deficit.

In many instances large lesions have been placed on the same side of the brain in both the globus pallidus and the ventrolateral portion of the thalamus. In such cases there has been no observable motor, sensory, or intellectual deficit. Thus, one may conclude that, in selected cases, relatively large portions of these structures in the basal ganglia may be sacrificed without interfering with voluntary motor movements or intelligence. The quantitative limits within which such procedures can be performed on both sides of the brain have not yet been established.

Placement of lesions in the thalamus is potentially more hazardous than placement of lesions within the pallidal complex because of the surrounding structures. If one places the lesion inferior to the ventrolateral nucleus of the thalamus, the corpus Luysi and its environs are penetrated and the possibility of production of hemiballismus is present. Immediately lateral to the properly placed thalamic lesion is the internal capsule, involvement of which will produce hemiparesis. Theoretically, placement of a lesion posterior to the posterolateral nucleus of the thalamus should result in sensory loss because of involvement of the sensory nucleus. However, in only two instances have we observed any gross sensory defect postoperatively in this group of patients. Moreover, in not a single instance have we observed the so-called thalamic pain syndrome following the placement of large thalamic lesions.

It is our impression that interruption of cerebellothalamic and other afferent systems to the thalamus, including pallidothalamic and rubrothalamic fibers, contributes to the relief of tremor and rigidity following placement of a lesion in this region.

The reversal of far advanced, completely incapacitating, progressive tremor, rigidity, and deformity, and in some cases dystonic symptoms, illustrates that parkinsonism and many of the other involuntary movement disorders heretofore considerel irreversibly progressive and hopeless need no longer be placed within this category. The five-year cure of the symptoms of tremor, rigidity, and deformity, even though other characteristics of the syndrome may persist, removes parkinsonism and certain allied disorders from the realm of hopeless incurable diseases. This statement is made not only to further the cause of surgical therapy of such diseases, but also because of the important medical implications of the reversibility of these heretofore progressive incapacitating symptoms. As a matter of fact, an objective analysis of the results of this study will demonstrate that parkinsonism, dystonia musculorum deformans, and certain related extrapyramidal hyperkinesias are now among the most treatable of all central nervous system diseases. An objective analysis of the results obtained in the investigation will demonstrate more consistently rewarding therapeutic effects than in similar large, concentrated series of intracranial arterial aneurysms, brain tumors, intractable pain, and several other categories of neurologic disease.

Because of the broad implications of these statements, we should like to mention a word

regarding their documentation. In 1955 Dr. Robert S. Schwab and Dr. Albert England of the Massachusetts General Hospital in Boston instituted an objective evaluation of our own cases of anterior choroidal artery and chemopallidectomy. Later, a mutual study was instigated, in which long-term cases from their clinic in Boston were operated by us and re-evaluated by Schwab and England. Their study of our cases corroborates conclusively that lasting complete relief of tremor, rigidity, and deformity is achieved by these technics without necessarily inflicting any neurologic or emotional deficit. Further, during the week of May 12, 1958, we brought back to St. Barnabas Hospital 100 follow-up patients who were operated upon for parkinsonism from one to more than five years ago. These patients were made available with their complete objective investigative records and cinematographic records for disinterested follow-up evaluation by any interested investigator.

One other clinical reference appears to be indicated at this time. The original classic description of the "Shaking Palsy" by Parkinson,[6] which led to the generally accepted syndrome which now bears his name, was based on his detailed clinical observation in six cases. The usefulness of adhering to the clinical description of this syndrome in the present day is highly questionable. The new therapeutic possibilities which exist in many cases of the shaking palsy requires intensive clinical study and selection by the clinician if the proper therapy is to be utilized. There is too little realization that any case which trembles is not necessarily parkinsonism. A restudy and reclassification of the various types of parkinsonism and the subdivisions of this syndrome would be useful, both therapeutically and in enhancing our ultimate physiologic understanding of the disease process.

Three large subdivisions which immediately come to mind are: 1) Cases with predominance of tremor and/or rigidity, accompanied by bradykinesia, deformity, and related motor symptoms. 2) Patients showing marked mental deterioration, such as presenile dementia accompanied by tremor and rigidity but actually predominantly incapacitated by the mental disorder. Paranoia is frequently seen in this group of patients. 3) The vegetative-akinetic type of patient, who demonstrates very little tremor or rigidity but is immobile, speechless, and usually handicapped by many vegetative symptoms. This particular classification is obviously somewhat naive. Nevertheless, it is readily apparent that it is in the first group of patients in whom surgical therapy is presently useful. The remaining patients, although demonstrating the syndrome of parkinsonism, are different from the first group.

One of the most interesting clinical phenomena observed in parkinsonian patients is the exaggerated physiologic response which many of these patients demonstrate to psychologic and physical stress. The initial onset of parkinsonian symptoms often follows an emotional or physical crisis. Moreover, extreme exacerbations of the disease may be precipitated by psychologic or stressful situations. Although we have observed this sequence of events frequently, we cannot explain it satisfactorily and feel that it deserves more thoughtful attention of clinicians.

CONCLUSIONS

A five-year follow-up study of more than 700 operations of anterior choroidal occlusion, chemopallidectomy, and chemothalamectomy leads to the following conclusions:

1. This investigation has resulted in a roentgen-anatomic-physiologic method of basal ganglia surgery which can relieve tremor and rigidity of parkinsonism in 80 per cent of properly selected cases, with a risk of mortality of 2.4 per cent and a risk of hemiparesis of 3 per cent.

2. Tremor, rigidity, deformity, and incapacitation of parkinsonism can be relieved without the infliction of any neurologic or psychologic deficit.

3. Five-year cures of the symptoms of tremor, rigidity, deformity, and incapacitation can now be documented in this series of cases.

4. On the basis of this study, parkinsonism can no longer be considered a hopeless, progressive, incurable disease. Inasmuch as the incapacitating symptoms of tremor, rigidity, and deformity have been alleviated by surgery of the globus pallidus and thalamus for as long as five years without recurrence, a more hopeful and realistically optimistic viewpoint can be adopted concerning this disease. The

therapeutic implications of this statement apply not only to surgical therapies but to the future development of medical treatment as well. Moreover, the symptoms of dystonia musculorum deformans have been alleviated during the course of this study for periods up to three years without recurrence. Thus, this disease can no longer be considered as necessarily incurable or irreversibly progressive.

5. The treatment of choice of many cases of parkinsonism and of all cases of dystonia musculorum deformans is surgery of the globus pallidus and thalamus.

6. Lesions confined to the globus pallidus and/or ventrolateral region of the thalamus on one side of the brain do not result in any motor, sensory, intellectual, or psychologic deficit. The extent to which such lesions can be inflicted on both sides of the brain requires further elucidation.

7. Clinical studies leading to a more physiologic classification of the subdivisions of the over-all parkinsonism syndrome are required if therapy and further basic investigations are to be conducted intelligently and fruitfully.

8. Many of the older concepts of basal ganglia function, pathogenesis of tremor and rigidity, and therapy of hyperkinetic diseases have been rendered suspect and some completely disproved by this and other investigations. There is a further need for evaluation of many concepts of extrapyramidal disease which have been allowed to become dogmatic and which do not concur with existing facts. However, not only must we be willing to re-evaluate former concepts, but we must also be on guard against replacing them with new dogmas too soon. Our entire understanding of the role of basal ganglia and the extrapyramidal system must be viewed in the context of the contributions of these structures to over-all brain function. Our present state of knowledge does not permit more than working hypotheses. These should not be misinterpreted as facts until they are proved beyond any doubt.

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Excitability in experimental myopathy

II. Potassium deficiency: an initial study

Gilbert H. Glaser, M.D., and Lawrence Stark, M.D.

A METHOD of studying excitability in muscle by measuring refractory period has been presented previously.[1] The sensitivity of the method was evaluated by determining the effect of quinidine, and application was made in an experimental myopathy induced by cortisone in rabbits. Since potassium depletion often is implicated as a cortisone effect and because of the many associations between body potassium fluctuations and muscular disorders in human clinical experience, such as potassium depletion in chronic nephritis and familial periodic paralysis, it was felt that a study of excitability in an experimental potassium deficiency would be indicated. Previous investigations[2,3] have delineated the histologic effects in skeletal and cardiac muscle produced by potassium deficiency in dogs and rabbits. The general occurrence of muscular weakness was noted, but specific studies of the physiologic disturbances in muscle were not made. Actual skeletal muscle necrosis may be induced by placing animals on potassium deficient diets. In rabbits specifically, the lesions, with segmental degeneration, infiltrations, and regeneration, are indistinguishable from those appearing in hypercortisonism.[3]

METHODS AND RESULTS

An initial group of 18 young rabbits ranging in weight between 1.0 and 2.0 kg. were given a potassium-deficient diet for 20 to 60 days. The diet, prepared by the National Biochemical Corporation, contained 64.2 per cent cornstarch, 30.0 per cent casein, 3.5 per cent butterfat, 1.3 per cent calcium carbonate, 1.0 per cent sodium chloride, and vitamin supplements. Three groups of six animals each were studied in sequence. Usually, generalized nonperiodic weakness and apathy appeared in the animals during the third week, followed by a rapid, progressive, muscular wasting and flaccidity, especially involving axial and proximal appendicular muscles. One to three animals in each group died relatively suddenly, unobserved, and without obvious cause usually at about 25 to 30 days.

Determinations of excitability in muscle were made by the technic of measurement of refractory period described previously.[1] In all instances the animals were unanesthetized and paravertebral muscles were studied. Bipolar stimuli were delivered through paired, single needle electrodes, and either coaxial needles or paired single needles were used for recording action potentials. A typical experiment is shown in figures 1 and 2, in which the time constant of the recovery curve of excitability is 3.6 msec. The animal had been on the potassium-deficient diet for 40 days. A final total of 12 surviving animals were studied, and the refractory period was found to be lengthened in all, with a prolongation of mean time constant to 3.4 ± 0.3 msec. This mean was increased from the 1.6 ± 0.1 msec. value determined in normal controls in the previous study.[1] The difference is significant at a p level of less than 0.01 (table 1).

The histologic lesions in skeletal muscles of potassium-deficient animals resembled those described previously by other investigators in dog and rabbit.[2,3] There was segmental degeneration of muscle fibers with loss of striations and invasion with macrophages. These lesions were spotty and associated with nearby apparently normal and regenerating muscle

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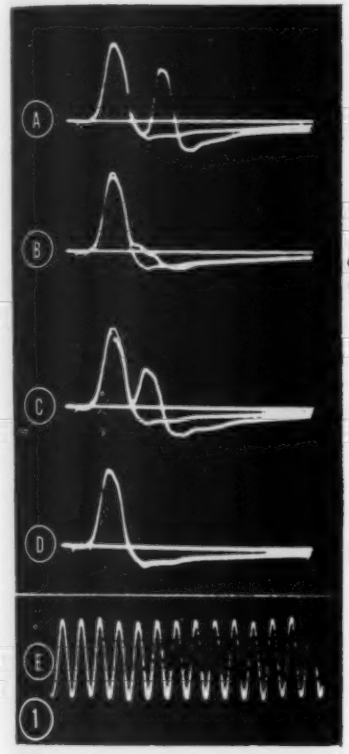

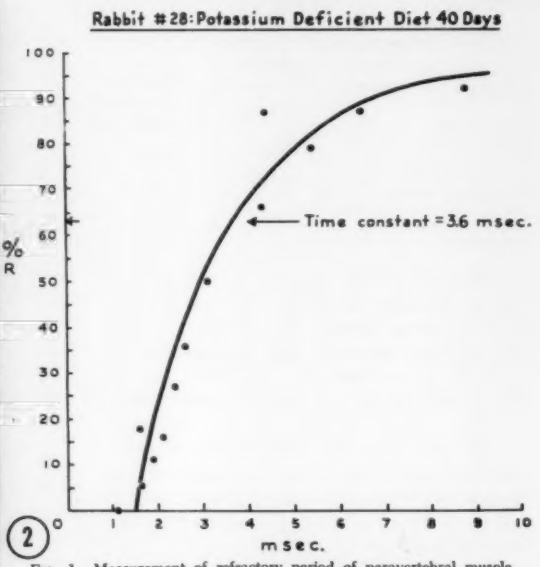

FIG. 1. Measurement of refractory period of paravertebral muscle of rabbit on potassium-deficient diet for 40 days. *A*, *B*, and *C*. Action potentials in relative refractory period. Diminished responses to second stimulus. *D*. Action potential at absolute refractory period. No response to second stimulus. *E*. Time calibration at 1,000 cycles per second.

FIG. 2. Recovery curve of excitability in paravertebral muscle of rabbit on potassium-deficient diet for 40 days. %R represents percentage of amplitude of second action potential as compared with the first. Abscissa in milliseconds represents time delay between stimuli determined experimentally.

fibers, the latter with numerous proliferating nuclei. In general, signs of regeneration appeared to be less prominent than in the myopathy induced by cortisone, but otherwise the picture was quite similar. These features are shown in figure 3.

It was not feasible in this series to determine adequately the intra- and extracellular potassium content of the skeletal muscles. However, plasma potassium level was reduced in most surviving animals by 25 to 30 per cent, a result similar to that observed in other studies of dietary potassium deficiency.[2]

COMMENT

In the present investigation it was found that rabbits given a diet deficient in potassium developed profound muscular weakness and wasting associated with segmental degenerative lesions. Refractory period of these muscles was increased significantly, indicating diminished muscular excitability. It is well known that potassium is involved in both excitatory and contractile processes in skeletal muscle, but the mechanisms and sites of these actions still have not been clarified.[4–6] However, increasing the ratio of intracellular to extracellular concentrations of potassium in muscle increases the resting membrane potential,[4] and this hyperpolarization has been related to decreased responsiveness of muscle to nerve stimulation.[6]

The lesions in muscles of potassium-deficient animals are regarded to be nonspecific and resemble those induced experimentally by hypercortisonism.[1,3] In addition, it had been determined[3] that an almost 25 per cent reduction in potassium content of striated muscles occurred in cortisone-treated animals. Despite the lesions and this chemical change, the refractory period in muscles of animals with cortisone myopathy was not altered from nor-

TABLE 1
REFRACTORY PERIOD TIME CONSTANT IN EXPERIMENTAL MYOPATHY
Potassium Deficiency

Experiment	*Time Constant (in msec.)*
Normal controls (12)	1.6 ± 0.1
Potassium deficiency (12)	3.4 ± 0.3*

*Different from normal controls at p 0.01 level of significance.

mal. In the present series of animals with induced potassium deficiency and similar segmental muscle lesions, the refractory period was markedly increased. This suggests that the method of measurement depends more on physiologic changes that cannot be correlated definitely with, or predicted by, histologic lesions. The particular mechanisms involved might be concerned with availability of potassium for muscular or neuromuscular excitability, which again need not be directly related to histologic changes.

In various clinical disorders in the human such as chronic nephritis and occasionally in treatment of diabetic acidosis, a lowered serum potassium occurs associated with muscular weakness.[7] Also, characteristically, there may be lowered serum potassium in familial periodic paralysis, although not always.[6,7] There is some evidence in this disorder that during attacks of paralysis there is a shift of potassium from blood into cells, at least in part into muscle, with a marked increase in absolute amount of intracellular potassium.[7,8] In addition, it is of interest that in myasthenia gravis there may be an elevation of muscle potassium during weakness and a fall occurring coincidently with improvement in muscle strength.[9] These relationships need further study, especially in those clinical instances of periodic paralysis wherein muscular weakness does not appear to be correlated with serum potassium variations. It is planned, therefore, to determine intra- and extracellular muscle potassium content in projected experiments with animals on a potassium-deficient diet and to correlate these levels with state of excitability in muscle.

FIG. 3. Paravertebral muscle of rabbit on potassium-deficient diet for 40 days, showing necrotic degeneration of muscle fibers and invasion with macrophages. Some regenerating fibers are present, with proliferating nuclei as well as apparently normal fibers. Hematoxylin and eosin stain. (x 350)

SUMMARY

An experimental myopathy was induced in rabbits by means of a potassium deficient diet. Measurements of muscle excitability by refractory period showed mean time constant of recovery curves to be 3.4 ± 0.3 msec., a significant prolongation from the normal value of 1.6 ± 0.1 msec. determined previously in control animals and in those with cortisone myopathy. The potassium-deficient animals showed severe muscular wasting and weakness grossly and segmental degeneration of muscle fibers along with some regeneration histologically, a picture similar to that seen in the previously studied cortisone myopathy. The changes in excitability, therefore, do not appear to correlate with histologic alterations. The significance of these observations and their relationship to other states of potassium deviation are discussed.

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■ The attacks of epilepsy are sometimes sudden; sometimes, as in apoplexy, they are preceded by certain premonitory symptoms, such as languor, torpor, pain or giddiness in the head, drowsiness, or disturbed sleep, dimness of sight, and tinnitus aurium. Besides these, many other precursors of epilepsy have been mentioned by authors. Among them, Aretaeus enumerates fulness and distention of the veins of the neck, and nausea and vomiting, especially after eating. Immediately before the fit, he says, flashes of light appear to the eyes, of purple, or black, or of various colours mixed together, as in the rainbow; there is a singing in the ears; disagreeable odours are perceived; and persons become bilious, and apt to be angry without cause.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Neurologic complications in patients with coarctation of aorta

H. Richard Tyler, M.D., and David B. Clark, M.D.

In one of the earliest papers on cerebral aneurysms Eppinger[1] reported a 15 year old boy who suddenly collapsed and died three days later. Postmortem examination revealed aneurysms of the anterior cerebral arteries and coarctation of the aorta.

Woltman,[2] reviewing the literature, noted that 32 cases of coarctation (approximately 7 per cent of the cases reported in the literature) had neurologic signs or symptoms, including headache, hemiplegia, convulsions, vertigo, tinnitus, transitory disturbances of vision, papilledema, mental disturbances, and complaints referable to the lower extremities. Since his paper, many isolated reports have appeared giving examples of neurologic complications of this disorder.

We have recently had the opportunity to review 200 patients with coarctation of the aorta seen at the Johns Hopkins Hospital, Harriet Lane Cardiac Clinic, and the Peter Bent Brigham Hospital between 1946 and July 1955, and we believe this group is of interest in helping to evaluate the isolated reports in their proper perspective.

Coarctation of the aorta is thought of as a rare entity. Its incidence in various autopsy figures has been estimated at 0.025 to 0.08 per cent[2–4] of the general population. Reifenstein[3] collected 104 cases age two years or older that had been autopsied at Boston hospitals and noted the average age at death was 47. The oldest reported was 92 years of age. In most series, males outnumber females by a ratio of about 4:1.[3,4] Table 1 summarizes neurologic findings encountered in our series. As can be seen readily, slightly over half of the patients had signs or symptoms that might require the attention of the neurologist.

CEREBRAL ANEURYSMS

There were three instances of proved cerebral aneurysms in our series. Two patients succumbed following subarachnoid bleeding, and one patient died following surgical removal of a large cerebral aneurysm.

Case 1. A 40 year old man had been known to have high blood pressure since age 20. One year prior to admission the patient had a convulsion. Following this he had severe headaches. From this time on he noted that vision was decreased in the left eye. His headaches had been present intermittently all year. Diplopia and ptosis of the left eyelid developed two months prior to admission. On physical examination the patient's left optic nerve was pale; his vision was 10/200. There was bitemporal hemianopsia, more complete in the upper quadrants. There appeared to be some erosion of the left anterior clinoid. On surgical exploration an aneurysm of the anterior communicating artery was found. Two months later he had a generalized convulsion and died shortly thereafter. Postmortem examination revealed a large aneurysm (3.5 by 2.5 cm.) of the anterior communicating artery, with rupture into the left frontal lobe and ventricular system. The diagnosis of coarctation of the aorta was confirmed.

Case 2. A 49 year old white man had a diagnosis of coarctation of the aorta at age 47. Two weeks prior to admission the patient fainted. Following this he had headaches. On the day of admission he was found unconscious with his right arm twitching and he was foaming at the mouth. He had Cheyne-Stokes respiration. Blood pressure in the arms was 200/100. His pupils were dilated and fixed. There were subhyaloid hemorrhages in both fundi. Knee jerks were present and brisk. Extensor tone was increased in all extremities, and there were bilateral extensor plantar reflexes. The neck was not stiff. Lumbar puncture showed an initial pressure of 530 mm. of water, with grossly bloody fluid. The temperature rose to 106° F. and the patient died. At postmortem examination the patient was noted to have a severe coarctation of the aorta. There was massive sub-

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arachnoid hemorrhage from an aneurysm on the left anterior cerebral artery. This had ruptured through the left frontal lobe into the ventricular system.

Case 3. A 41 year old white female had always complained of cold feet. As long as she could remember, she had had to rest after walking two or three blocks because of painful legs. At age 36 the patient began suffering from left-sided headaches. At age 40 she had a generalized convulsion, followed by a transitory aphasia. Since that time she had had two or three convulsions per week. Sometimes these episodes were followed, or preceded, by tingling of the right arm and leg. Physical examination revealed a well-developed, well-nourished female. Blood pressure was 200/100 in the arm, 0/0 in the leg. Except for decreased arterial pulsation in the lower extremities, physical examination was normal. Neurologic examination revealed a normal mental status. Cranial nerves were normal. Speech was noted to be dysarthric. She had a mild awkwardness and apraxia of the right hand. No disturbances appeared in sensory or reflex examination. Angiography revealed a large saccular aneurysm on the middle cerebral artery. An electroencephalogram showed a slow-wave focus in ished female. Blood pressure was 200/100 in the arm, 0/0 in the leg. Except for decreased arterial pulsation in the lower extremities, physical examination confirmed the diagnosis of coarctation of the aorta. There was no other aneurysm present on the cerebral vessels.

Two other patients probably had cerebral aneurysms. No angiographic studies were done. The first patient was a 30 year old man who had headaches for a period of two years and suddenly developed a sixth-nerve palsy in association with a severe headache. The second was an 11 year old boy who suddenly lost consciousness and on recovery had a severe occipital headache and right-sided weakness. He had bloody spinal fluid under increased pressure. Two years later he died suddenly without autopsy.

TABLE 1

Coarctation of the Aorta (200 Cases)
Neurologic Signs and Symptoms

1. Cerebral aneurysm	Proved	3
	Probable	2
2. Cerebral infarction		3
3. Loss of consciousness		6
4. Headaches		50
Migraine		8
5. "Numbness"—left hand		3
6. Complaints in lower extremities (preoperative)		
Pain and cramps		18
"Going to sleep"		29
Spinal cord insufficiency		7
7. Incidental		1
Total number of patients		103

In our series there were 125 patients above the age of ten. Since no ruptured aneurysm has been reported below that age in patients with coarctation, the corrected incidence in our series was 4.0 per cent. Most of these patients are still alive at the time of writing; therefore, the final incidence will be higher.

Eppinger[1] reported the first example of ruptured cerebral aneurysm with coarctation, and since that time 23 other examples have been reported.[1–30] Cerebral aneurysms as incidental findings in patients with coarctation who died of other causes have also been noted.[8, 30–34] Subarachnoid hemorrhage without definite identification of an aneurysm was seen in some cases.[9, 28, 35–37]

The size of the aneurysm has often been very large.[4, 14, 26–29, 35] A large number have been on the middle cerebral artery. The average age at time of death or rupture has been 25, with an age span of 12 to 77 years.

This is the only form of congenital heart disease with which aneurysm is correlated, except possibly of patent ductus arteriosus.

CEREBROVASCULAR ACCIDENTS

Kriegk[7] reported two examples of cerebral hemorrhage in a boy of 11 and a girl of 28. Moon[38] and Fisher[33] reported similar instances. No evidence of aneurysm was present in their cases, and it appears likely that they are examples of hypertensive hemorrhages. These cases occurred in the second or third decade of life. In our series there were no instances of cerebral hemorrhage.

De Amalgro[39] cited the case of a 19 year old girl who developed a sudden left hemiparesis and had a cerebral softening which was believed to be embolic in nature. Similar cases have been reported by others.[35, 38, 40, 41] The embolus was noted to come from a clot which had formed in an aneurysmal dilation of the aorta above the coarctation, in or on an arteriosclerotic plaque. Most of the patients reported were in the third or fourth decade of life.

There were three examples of a cerebral infarction in our series.

Case 4. A five year old boy had a history of pneumonia at age nine months. A large heart was

noted and coarctation of the aorta was diagnosed. The patient developed cardiac decompensation during the episode of pneumonia and was noted to have a left hemiplegia. When seen at age five, he had an infantile hemiplegia of moderate degree.

Case 5. An 11 year old boy had headaches for an indefinite period. Hypertension was noted on routine examination, and coarctation was diagnosed. The patient had a successful resection of the coarcted segment of the aorta. During the procedure the subclavian artery on the left was ligated. One month later, while playing baseball, the patient became suddenly ill and vertiginous and vomited. Physical examination revealed a drowsy child. No meningeal signs were present. The fundi were normal. There was nystagmus on gaze to the left. The rest of the other cranial nerves were intact. There was intention tremor of the left hand and foot. There was a slight left-sided hypotonia. Reflexes were decreased on the left side and the patient's right plantar was extensor. Lumbar puncture revealed a pressure of 180 mm. of water, with normal cytology and a protein of 30 mg. per cent. The patient recovered and was left with only minimal cerebellar signs when seen two years later.

Occasionally, a thrombus will form at the anastomotic site and serve as a source of emboli. One such case is abstracted below.

Case 6. A 13 year old boy exhibited high blood pressure (170/80) on a routine physical examination and diagnosis of coarctation was confirmed by angiography. The patient had the coarcted segment of the aorta removed. Three hours later he was found to have a right hemiplegia, with eyes turned to the left. The reflexes on the right decreased, and there was a right extensor plantar reflex. Lumbar puncture revealed a pressure of 310 mm. of water; protein and cytology were normal. The following day the patient showed signs of a partial third palsy, with a large left fixed pupil and the left eye elevated laterally. He died 24 hours following operation. Postmortem examination showed a thrombosis in the suture line in the aorta and emboli in the left carotid and middle cerebral vessels. The left hemisphere was swollen, and there was a large uncal herniation. Microscopic section showed changes of early infarction.

The most important cause of cerebral infarction in patients with coarctation is subacute bacterial endocarditis. Its importance lies predominantly in the fact that it is potentially a curable disease which is overwhelmingly fatal if left untreated. There was a single example in our series. The following case is a typical example of special interest in that the diagnosis of coarctation was made as the investigation for the cause of emboli and subacute bacterial endocarditis was being undertaken.

Case 7. A 17 year old white male had been healthy, athletic, and active until nine weeks before admission when he developed chills, fever, night sweats, and epistaxis. He was treated with two million units of penicillin for two days. One day previous to admission he had a right-sided seizure, followed by right hemiplegia, aphasia, and a temperature of 103° F. Lumbar puncture revealed 800 polymorphonuclear cells. He was transferred to the Peter Bent Brigham Hospital for further evaluation. Temperature was 100.8° F.; blood pressure (L) 180/84/10, (R) 178/78/10 in the arms and 128/0, 130/0 in the legs. He had petechiae, right hemiplegia with increased reflexes, and an extensor plantar response. Lumbar puncture showed an initial pressure of 230 mm. of water; fluid cloudy, with 180 cells; 80 per cent polymorphonuclear cells; and 20 per cent leukocytes. No organisms were seen. Four blood cultures were positive for *Streptococcus viridans*. The patient received a course of antibiotic therapy and improved slowly. He was left with a residual aphasia and hemiparesis. One year later he had a successful operation to correct the coarctation. At this time he could use his right arm and leg reasonably well but preferred his left in many common uses. He had a residual aphasia. He had one convulsion nine months after his initial episode and was placed on anticonvulsant medication.

SYMPTOMS IN THE UPPER EXTREMITIES

Three patients developed complaints of numbness and tingling in the left extremity. In one patient it was correlated with changes in position, but in two patients there was no such correlation.

Case 8. A 41 year old man had noted for one year that, on putting objects overhead or putting his left hand behind his head, his left arm and hand became numb. It usually took a few minutes to recover. The patient was operated on and coarctation was noted to be just below the left subclavian artery. Following resection, the patient had no further complaints referable to the arm.

In all these patients, the coarctation was just distal to the origin of the left subclavian artery. It is presumed that there was some physiologic mechanism which interfered with normal circulation of blood to the left arm in these cases and that there was secondary vascular insufficiency to the peripheral nerves in the upper extremity. It is suspected that this occurs in relation to the thoracic outlet. Unfortunately, none of the patients was seen at the time of symptoms, but neurologic examination was normal in all three when examined subsequently. Coarctation has been known to occur

with either atresia or stenosis of either subclavian artery.[42*]

SYMPTOMS REFERABLE TO THE LOWER EXTREMITIES

There were complaints referable to the lower extremities in 54 of our patients (25 per cent). The most common complaint was pain or cramps developing after exercise or walking (18 patients). This almost certainly was secondary to vascular insufficiency in the lower extremities, primarily affecting circulation in muscles.

A number of patients noted that their legs "went to sleep" if they kept still or lay quietly in bed (nine patients), while others had a similar complaint after exertion (eight patients). One patient, for example, noted that his legs became "numb" and "tingling" whenever he had to run for a bus. Also noted by some patients (12 patients) was the ease with which a leg or foot might "go to sleep" if they crossed their legs. Similar cases have been noted by Lebert,[43] Redenbacher,[11] Sommerbrodt,[8] Leyden,[44] and Moon,[38] and others.[10] In Zhar's[16] case there was actually an ischemic necrosis of the limb.

One case was of special interest in that it was probable that the patient's complaints were attributable to vascular insufficiency primarily affecting the spinal cord.

Case 9. A 28 year old man was perfectly well until age 18, except for occasional headaches. During a 100-yard dash in high school, his lower extremities felt "numb" for about ten minutes but he was able to get up after a minute or two and walk. On one occasion at age 19 he noted some difficulty in breathing following a large meal. He began to run and again felt "numbness and tingling." He fell, but was able to get on his feet immediately.

At age 23 he was told he had high blood pressure and a heart murmur. A diagnosis of coarctation was made. Since then, he has had rare occipital headaches and has had frequent attacks of numbness in the lower extremities.

Physical examination revealed blood pressure 160/90 in the arm, 0/0 in the legs. Neurologic examination was significant in that there was absence of both knee and ankle jerks and the plantar responses were flexor. There was a slight and diffuse motor weakness of the lower extremities. No fasciculations or wasting was noted. Sensory examination was normal. He had a surgical resection of the coarctation and, except for inability to void for ten days, had an uneventful convalescence.

Six other patients in the series noted "heaviness" of the lower extremities following exertion. They were unable to define this further.

Woltman[2] reported a similar example in a clinically diagnosed case of coarctation. Taussig[10] noted that "numbness and coldness of the lower extremities is not uncommon. Some patients complain of weak legs. Occasionally a patient complains that strenuous exercise produces muscle cramps."

LOSS OF CONSCIOUSNESS OR CONVULSIONS

There were six patients in the series who gave a history of loss of consciousness or convulsions which was not clearly related to a cerebral hemorrhage or a cerebrovascular attack. One patient had many convulsions in the first ten days of life and was left with a minimal right hemiparesis. Brain injury secondary to a difficult birth seemed to be the etiologic cause in this case.

The other five patients all had associated cardiac abnormalities (septal defects) which may have contributed significantly to the pathogenesis of the spells. In all patients these episodes occurred between the first and fourth year of life and then disappeared. They were all similar in that they were precipitated by exertion, excitement, or hard crying, and the child would stiffen out into an opisthotonic position and lose consciousness. The eyes would roll up, though none had convulsive movements. The attacks lasted from ten seconds to three minutes. In two patients in whom electroencephalography was performed (during the same week that an attack had occurred) normal records were obtained. The mechanism of these episodes is probably similar to the loss of consciousness seen after breath holding in some normal children or secondary to altered hemodynamics.

HEADACHES

Headache was a prominent symptom in 50 patients. The actual description of the headaches was quite varied. The most common complaint was a frontal or occipital dull throbbing headache which was present on

*Plum and Wyburn-Mason, at discussion of this paper when presented at the American Academy of Neurology in Philadelphia, April 26, 1958, noted patients with aneurysmal dilation of vessels in the spinal canal which could account for their symptoms. One patient had signs of spinal cord damage.

or shortly after awaking and diminished gradually during the day. It usually responded to salicylates. In five patients there was a definite relation to exertion. Many of the patients noted dizziness and tinnitus in association with the headaches. Eight patients had hemicranial headaches which were associated with auras and usually nausea and vomiting. In these patients the headache was not always on the same side, nor was there any preference for one side.

Coarctation appears to be the only form of congenital heart disease with a high incidence of migraine-like headache.[46]

INCIDENTAL NEUROLOGIC COMPLICATIONS

One patient with myasthenia gravis was found in this series.

Approximately 25 per cent of patients die as a result of rupture or dissection of the aorta. No instances of secondary neurologic complications have been noted in our series or in the literature, although neurologic complications might be expected in some cases.

Meningitis secondary to subacute bacterial endocarditis has been reported,[16] and one would anticipate that patients with coarctation might be susceptible to all the neurologic complications of subacute bacterial endocarditis. The frequency of cardiac anomalies, bicuspid aortic valves, and the like, is high in these patients, and almost 25 per cent of them succumb to subacute bacterial endocarditis.[3]

DISCUSSION

The occurrence of neurologic signs and symptoms is often the first clue to systemic illness. This is true in patients with coarctation of the aorta, as is apparent from a perusal of the case histories given in the preceding portion of the paper. These patients have often been seen first by a neurologist and the underlying disorder has been discovered only when the possibility of coarctation has been entertained and the necessary confirmatory signs are checked for. In most instances this is extremely simple and requires measuring the blood pressures in both arms and legs, as well as the quality of the pulses in the four extremities. In all but the most unusual cases, this will alert one to the possibility of an aortic lesion.

Patients may present any of the complications previously enumerated. Since coarctation of the aorta is a form of congenital defect in which corrective cardiac surgery can often be performed, there is added benefit if cases are discovered before irreversible changes have occurred.

Coarctation may occur alone, though it is often associated with defects in cardiac valves and other congenital abnormalities.

The incidence in this series would suggest that there are almost 150,000 patients with this abnormality living in this country alone. This is comparable to the incidence of many diseases which the neurologist sees frequently within his specialized practice and suggests that most of the cases of aortic coarctation have not been recognized clinically.

In the two years since the senior author has studied this relationship, he has had the opportunity of seeing three patients with neurologic symptoms, referred to him by an internist, where the diagnosis of coarctation has been made. This would suggest that such patients actually are passing through neurologic clinics and are seen during ordinary neurologic practice.

At operation for correction of the coarctation in these cases, there was no striking variation noted in the great vessels arising from the aortic arch. There were a few congenital variations, but these were similar to that which could be expected in a normal population.

There has been much debate in the last few years as to whether aneurysms are congenital or secondary to arteriosclerosis. Our material was not suitable or extensive enough to evaluate this important point.

Aneurysms have been noted to occur in conjunction with other systemic diseases, such as polycystic kidney disease, polycystic liver disease, periarteritis nodosa, and so on. In these illnesses there is usually coincidental hypertension or direct involvement of the vessel at the site of aneurysmal formation.

We have no good explanation for the increase in vascular migraine-like headaches seen in these patients. We have had the opportunity of reviewing over 2,000 cases of cardiac abnormalities of other types, and this type of headache has been seen more often with this condition than in any other.

The complaints referable to the lower extremities are of major interest in that they are exceedingly frequent and their presence in a patient also subject to headaches should alert one to the possibility of coarctation of the aorta. In themselves, they do not appear to be specific, and similar complaints can be elicited with great frequency in elderly patients who are suffering from vascular disease of the major vessels.

SUMMARY

A review of the neurologic complications encountered in 200 patients with coarctation of the aorta was made. The previously noted high incidence of cerebral aneurysms was confirmed. Cerebrovascular accidents are not uncommon. Cerebral hemorrhages are usually secondary to severe hypertension. Emboli are secondary to thrombi which form in an aneurysmal dilation proximal to the site of coarctation or to subacute bacterial endocarditis. Symptoms are frequent in the lower extremities and are probably secondary to the deficient vascular supply. Loss of consciousness or convulsions were not seen in uncomplicated coarctation. Headaches were extremely frequent in these patients and often were the major symptom. The fact that these patients are frequently seen by neurologists is suggested, and the need to keep this cardiac abnormality under consideration in certain cases is stressed, since many such patients are amenable to surgery.

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■ In a few instances the spinal cord has been found to be so much enlarged, apparently by a true hypertrophy of its natural tissues, as to occupy the whole space of the vertebral canal; but most generally what seems to be hypertrophy at first sight is due, chiefly at least, to congestive swelling and oedema. True hypertrophy has been met with in the foetus: it occurs mostly in children: and it presents, so far as is known, no symptoms by which it can be recognized. Hypertrophy of the brain is a very uncommon affection, but it is common as compared with hypertrophy of the spinal cord.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

A simple device for measuring the visual motor reaction time

Robert S. Schwab, M.D.

About three and a half years ago we endeavored to apply the usual reaction time technic to patients with parkinsonism. The test used a neon light and a standard key which was pressed by the subject when the light went on. The interval of the motor reaction time was indicated on a moving paper strip.

Observations were completely unsatisfactory, because the patient would accidentally contact the key due to the presence of tremor of the finger. Various complicated electronic circuits were considered and explored which would eliminate this, but nothing economical or practical was achieved.

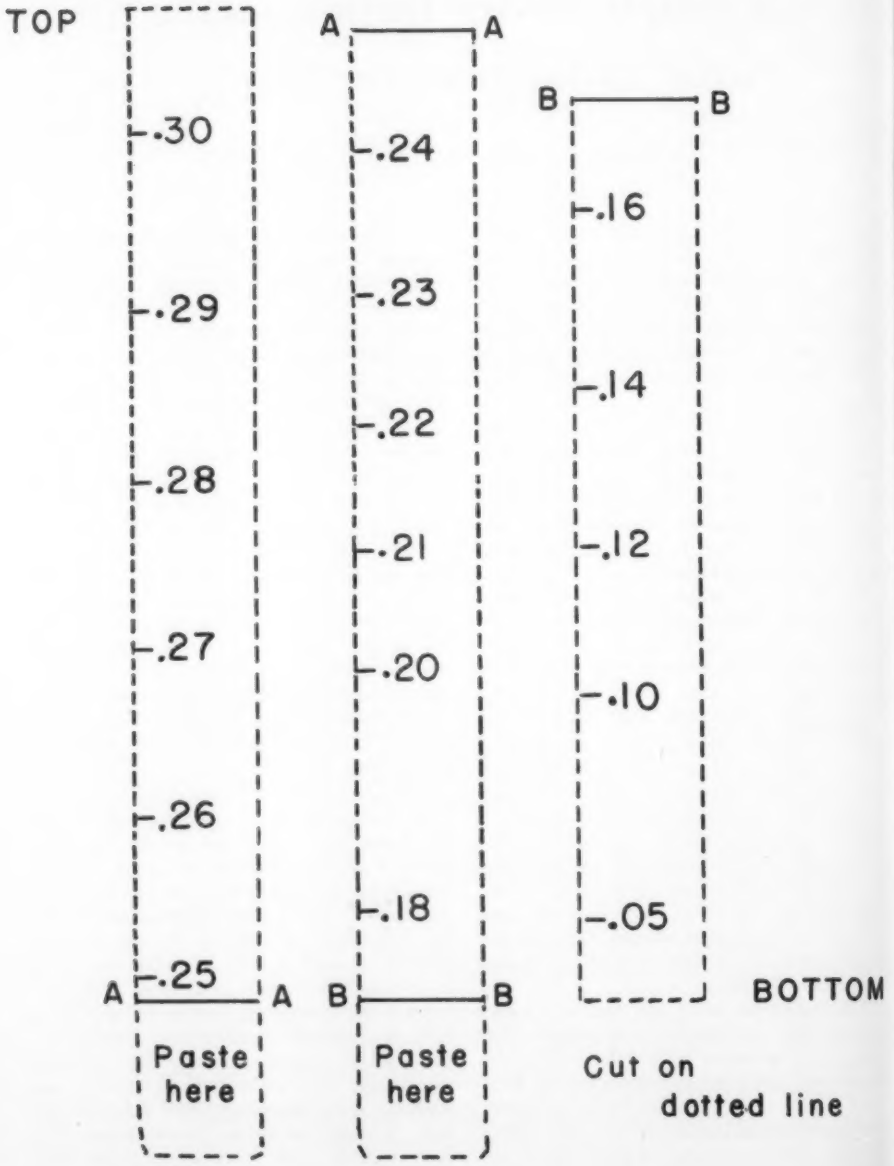
Finally, a very simple dropping bar system was devised. This became eminently satisfactory and has been used routinely in the regular examination of patients with this disease during the past three years.

An aluminum bar 18 in. long and ¼ in. thick and 1½ in. wide forms the basis of the apparatus. Beginning at one end, lines are made from the calculations of the falling body formula. These are illustrated on the diagram in figure 1. It is seen that the first half-inch that the bar falls takes 0.05 seconds, and the entire bar will fall its 18 in. in a little over 0.3 seconds. The formula $\frac{1}{2}GT^2$ = distance was used, where T is the time in seconds, G is 32, and the answer for each time element is in inches or fractions thereof.

The technic of using this bar in a motor reaction time examination is as follows. The subject, either sitting or standing, holds his thumb and index finger approximately ¾ in. apart. The bar is suspended by the observer, holding the top end (approximately ¾ in. above the mark .30) so that its lower end (⅛ in. below the mark .05) is between the finger and thumb of the subject being tested. The subject is instructed to watch the bar closely and to close his finger and thumb over the surface of the bar at the first beginning of movement. The bar is released by the observer and the subject grabs it. The point where his finger and thumb hold the bar represents the duration of the motor reaction time and can be read off directly in decimals of a second. It is usual for the first effort on the part of a subject who is not familiar with the test to be a little slow, but the second, third, and fourth attempts are close enough to give a good average of the values sought. It is important to be sure that the subject watches the bar and does not watch the face of the observer, who might give away what he was about to do in some anticipatory change in expression, so that the subject could start his finger movements before the bar was actually released. This is not an actual problem, because such a maneuver produces ridiculously low values, and this has not been a problem in our routine use of the bar.

The reaction times obtained in this manner were compared with those obtained in the usual key light system and do not vary from these at all. The presence of tremor or other involuntary movement does not interfere with this test. It can be used for either hand without difficulty. In running through a large number of normal subjects, none were able to demonstrate shorter times than 0.16 of a second, the average in normals being 0.18 to 0.21 of a second. Interestingly enough, patients with parkinsonism, with their apparent exceedingly slow movements in walking and dressing, show surprisingly little deficit in this test. Average values in parkinsonism cases were 0.22 to 0.26. Very severe cases have

From the Parkinson Clinic, Massachusetts General Hospital, Boston.


TOP
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BOTTOM
Cut on dotted line

Figure 1

longer reaction times, but rarely are these over 0.30. Successful handling of these patients improved the reaction time slightly.

When dealing with subjects who are rather slow in understanding what to do (defective), it is well to drop the bar clear of the foot of the subject and have a rug or towel on the floor so that it does not damage the edge of the falling instrument.

Since it may be difficult to get these aluminum bars inscribed with the correct lines and numbers, it is suggested that readers who are interested in obtaining one cut out the three 6-in. sections of the scale and paste them together so that the A's and B's are superimposed. This should give an 18-in. strip which may be pasted on an aluminum bar such as described previously, or on an 18-in. standard steel ruler. The aluminum bar mentioned weighs 4¾ ounces, an 18-in. stainless steel ruler weighs 2¼ ounces, and an 18-in. wooden ruler weighs 3 ounces. Any of these will be satisfactory.

After the paper has been accurately glued to the bar or rules, it can be covered with Scotch tape or shellac to give it more or less permanent status. The standard steel rulers have a thin felt strip on the other side, which is useful in preventing the stainless steel surface from slipping between the fingers. We have not found it necessary to paste a felt strip to the aluminum bar, which slips very little, but this can be done if desired. It is obvious that, whether the bar is made of stainless steel, aluminum, or wood, it falls at exactly the same rate. The important factor is that it be light enough so that the simple finger pressure of a subject will stop its fall instantly.

■ I now speak of convulsion beginning unilaterally (which is, I think, the mobile counterpart of the unilateral palsy just mentioned) in more detail. These convulsions—sometimes called epileptic, but oftener epileptiform—may begin in the face, in the arm, or in the leg. I think it is a matter of some significance that they usually begin in the arm (this part usually suffers more in hemiplegia), and, when so beginning, the hand is the part of this limb nearly always attacked at the onset, and mostly —this is my experience—the thumb and index finger are those of the digits which suffer first.

J. Hughlings Jackson in *Notes on the Physiology and Pathology of the Nervous System*, published in 1868.

CASE REPORT

Hemorrhage as a complication of subdural puncture

Joseph V. McDonald, M.D.

NEEDLE PUNCTURE of the subdural space in infants is now commonplace to diagnose and treat hematomas and effusions. Evidently, complications are few. For that reason, it was thought worthwhile to record the following case in which a serious hemorrhage occurred during aspiration of a subdural effusion associated with meningitis.

CASE REPORT

On January 21, 1957, a 6-month-old boy was admitted to Strong Memorial Hospital because of a high fever. The child had a right otitis media in November 1956. This drained spontaneously for a day and during the next two months recurred and again drained twice more. In December 1956 there was an episode of fever (103° F.), irritability, and twitching which may have been a generalized seizure. The baby was treated at home by his family physician. He recovered and remained well until January 12, 1957, when he became febrile and again had purulent drainage from his right ear. For four days he received penicillin but the fever persisted. He became lethargic and lost his appetite. On the morning of January 21, 1957, while he was being fed, his mother noticed that he stared into space and then had jerking movements throughout his right side. Arrangements were made for hospitalization.

On admission to the hospital, he was pale and lethargic and appeared seriously ill. He could not sit alone. The tonus on the left was greater than that on the right, and brief episodes of clonus occurred in the left arm and leg. His temperature was 36.5° C., pulse 140, weight, 9,720 gm., head circumference 44.5 cm., and chest circumference 46 cm. The fontanelle was soft. The pupils were round, regular, equal, and reacted to light. Most of the time the eyes were deviated to the left.

The left ear drum could not be seen, but in the right drum there was an acute perforation of moderate size.

The examination of the chest and abdomen was unremarkable. The deep tendon jerks were normal in the arms but hyperactive in the legs. There was no nuchal rigidity. He responded only slightly to painful stimuli.

Roentgenograms showed no aeration of the mastoid cells. There was questionable widening of the coronal and sagittal sutures. A chest film showed increased bronchovascular markings, with no pneumonic infiltrations.

A lumbar puncture was done. The fluid was slightly turbid and contained 383 white blood cells per cu. mm.; 50 per cent of these were mononuclear cells. The fluid contained 225 mg. per cent protein; 123 mg. chloride per liter, and 61 mg. per cent sugar. No organisms were seen in a smear and none could be cultured. Cultures of blood and nasal secretions were also negative. Parenteral therapy with chloromycetin, penicillin, and sulfapyridine was begun.

On January 22, 1957, bilateral subdural taps were done through the coronal suture. On the left side no fluid was obtained. On the right side 5 cc. of slightly xanthochromic fluid was removed. This contained 11 white cells per cu. mm. and had the following characteristics: protein, 55 mg. per cent; chloride, 113 mg. per liter; sugar, 13 mg. per cent. Cultures and smears were negative.

His general condition improved during the day, but at 11:30 p.m. it was noted that he was not moving his right side.

On the following morning a right subdural tap was done but yielded only a few drops of fluid. On January 24 he had two right-sided jacksonian seizures which began in the face. Lumbar puncture yielded clear fluid containing 55 cells, 74 mg. protein, 130 mg. chloride, and 32 mg. per cent sugar. Both gram smears and cultures were negative.

He was seen by a neurosurgeon for the first time on January 25. It was recommended that bilateral subdural taps be repeated. On this occasion 12 cc. of clear yellow fluid were removed from the left subdural space and 15 cc. from the right. Smears and cultures were negative. On January 26 the taps were done again. On the left

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FIG. 1. Photograph showing the medial portion of the hematoma in the forceps and the vein running from the clot to the superior longitudinal sinus, which lies beneath the towel on the right. The brain is covered with cottonoid.

7 cc. of clear fluid were obtained and on the right, 12 cc. On January 27 a right subdural tap yielded 8 cc. of faintly xanthochromic fluid and the left, 2 cc. of bloody fluid. It was noted that the child was alert and in good condition and sucked well. At 6:00 p.m. on January 28 a left subdural tap again yielded only a few drops of fresh blood, while the one on the right yielded 15 cc. of xanthochromic fluid.

At 4:00 a.m. the next day he took his feeding poorly. One hour later a student nurse recorded that he was very pale. On rounds about 10:00 a.m. he was found to be in a coma. The left pupil was dilated and fixed and there was ptosis of the left eyelid. The right pupil responded to light. The fundi were normal. On the right side the arm was spastic and the leg was flaccid. There was a Babinski sign on the right side and clonus at the ankle.

The hematocrit, which had been 28, was found to be 11, and a left subdural tap yielded 12 cc. of fresh blood. The child was taken to the operating room where a thick tenacious blood clot was found beneath left frontal and temporal burr holes. In order to remove it, a left frontoparietal bone flap was turned down. There were no membranes over the clot, which covered all but the occipital portion of the hemisphere. At a point just beneath the lateral margin of the anterior fontanelle, a large vein was found running from the clot into the superior sagittal sinus (figure 1). This vein was doubly ligated and cut. The solid hematoma was then removed. No active bleeding point was found. Some clear subdural fluid was removed through a temporal burr hole on the right side, but there were no memberanes. During the day the child received 800 cc. of whole blood. That night the hematocrit was 28.

The pathologic diagnosis was acute subdural hematoma. Microscopically, all sections showed recent blood clot without significant organization. There was some compressed fibrin on the surface in several areas.

By evening, the baby was moving the right side voluntarily. He made a rapid recovery thereafter and was discharged on February 10. At that time he still had a right hemiparesis which was resolving. His weakness has since disappeared and he now uses both sides equally well, although he has required anticonvulsants to control right-sided seizures.

DISCUSSION

In this case, it seems obvious that the vein shown in figure 1 was torn during the needling of the subdural effusion. On the last two occasions on which punctures were made, only blood was obtained on the left side. Probably this should have been taken as a warning of danger. As Guthkelch[1] has pointed out, if an effusion dries up suddenly instead of gradually, it may have become loculated and hence inaccessible to a needle introduced through the coronal suture.

While a hemorrhage as large as the one in this patient is fortunately very rare, it is not uncommon for even an experienced operator to obtain a few drops of fresh blood when performing a subdural puncture. Usually such bleeding is disregarded because it stops readily and is of small volume. However, it would seem likely that the addition of fresh blood

to a hematoma or effusion would increase its size, both directly by the amount of blood added and indirectly by the osmotic force of the newly added blood pigments derived from the breakdown of the fresh hemoglobin.

Ingraham and Matson[2] mentioned that, on the rare occasions when postoperative subdural taps must be done because of a reaccumulation of fluid, "If further bleeding occurs into this fluid, new membranes may form." They make no mention of the effect of such bleeding into hematomas before surgery.

The need for postoperative needle puncture rarely arises, except in cases where the hematoma has been present for some time and the degree of brain atrophy is quite marked. Almost invariably, when exposed by burr holes or a flap, the volume of a subdural hematoma is quite a bit greater than the 10 or 15 cc. which is usually removed by needle puncture. Therefore, even though the child improves symptomatically during daily tappings, there remains over the surface of the brain a collection of fluid sufficient to depress it and contribute to the further formation of membranes. The hematomas which disappear on repeated puncture are ordinarily only the small very early ones.

Probably because so few children with these hematomas die now, there is remarkably little information concerning the state of the brain beneath them. The fact that the cortex expands to fill the dead space is no guarantee of normalcy. Air studies done on children who have had subdural hematomas and who have had persistent seizures often show moderate to marked ventricular dilatation as well as some cortical atrophy. That the brain beneath a hematoma may be badly damaged has been demonstrated by Phillips,[3] who described very severe cortical softening as well as gliosis of the white matter in the brain of a 4-month-old infant who died following a craniotomy and 54 days of aspiration for a subdural hematoma. Phillips ascribed these changes to compression of both the cortex and its nutrient vessels by the hematoma and pointed out that removal of the subdural membranes would be only an empty gesture in such cases.

Nevertheless, many physicians are loath to move on to the next logical step of burr hole exploration after needling a hematoma for a few days. Some fear the supposed magnitude of the procedure and favor a "conservative" approach, despite the fact that there are definite dangers to prolonged needling of subdural hematomas. One may inadvertently cause fresh bleeding into them or may permit compression of the brain to exist for an unnecessarily long period of time. Therefore, in all chronic subdural effusions and hematomas, surgical exploration and drainage of the subdural space should be done as soon as the patient can withstand the operation safely. This point is often overlooked after the diagnosis has been established, because the child makes great symptomatic improvement on simple needle aspiration. As Hankinson and Amador[4] pointed out in their discussion of infected subdural effusions, "It is inadvisable to persist in the simpler type of treatment for more than a few days." Ingraham and Matson[2] stated that all infants who have excessive amounts of fluid recovered from a subdural hematoma or effusion should have an exploration done to make certain whether or not membranes are present.

CONCLUSION

A case of massive hemorrhage in an infant, caused by needling an effusion, is reported.

Several reasons are given for encouraging earlier surgical exploration of subdural fluid collections in infants.

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Neurology

BOOK REVIEWS

The Functional Organization of the Diencephalon

W. R. Hess. A summarized English translation, edited by John R. Hughes, under the auspices of the National Institutes of Mental Health and Neurological Disease and Blindness. 1957. New York: Grune and Stratton, Inc. 180 pages. $7.00.

The reviewer remembers the profound impression which the reading of Professor Hess' programmatic papers of 1924 and 1925 had made on him some 28 years ago. (Schweiz Arch. Neurol. u. Psychiat. 15:260, 1924; 16:36 and 285, 1925). It is a pity that these papers, in which the basic framework of Professor Hess' thought and the subsequent long investigations were so beautifully stated, are not available in English translation.

The present volume makes available the English translation of the results of 25 years of systematic, electrical exploration of the diencephalon published by Professor Hess in 1949 under the title "Das Zwischenhirn," as a companion volume to his "Die Funktionelle Organisation des Vegetativen Nervensystems" which appeared a year earlier. Professor Hess' lectures delivered at Harvard Medical School in 1925 on "Diencephalon. Anatomical and Extrapyramidal Functions" were published by Grune and Stratton in 1954.

The present English translation of "Das Zwischenhirn" consists of three parts. The first part deals with the hypothalamus and autonomic functions, and the second part with the extrapyramidal motor functions and the diencephalon. In the third part description and discussion of Professor Hess' experimental method with instructions on technics of its application are presented. The book is illustrated with an atlas of diagrams of serial sections of the cat's brain, with detailed designation by symbols of the loci of stimulation and of the behavioral effects. A list of bibliographic references from the second German edition is added to the English translation. There is a six-page subject index.

P. I. Y.

Chemistry and Biology of Mucopolysaccarides

Edited by G. E. W. Wolstenholme and Maeve O'Connor. Ciba Foundation Symposium. 1958. Boston: Little, Brown and Co. 323 pages. $8.50.

This volume is the latest in a series of publications of symposia held under the auspices of the Ciba Foundation in London. This symposium was held in April 1957 under the chairmanship of Professor W. T. J. Morgan and represents an ambitious program which brought together outstanding investigators from Europe, North America, and Australia to discuss the multifaceted subject of mucopolysaccharides. The participants recognized that the mucopolysaccharides are not a well-defined group of substances, so that the formal papers and discussions embrace a wide range of carbohydrate-containng complexes and the relatively simple molecules of which they are composed.

This is not an easy book for the clinical neurologist or the neurologic investigator to read. Both papers and discussion are highly

technical, presupposing a fair knowledge of the general field and dealing with many investigative areas not familiar to the majority of neurologic scientists. Nevertheless, the inquisitive reader will be rewarded in two ways, first, by learning what an inclusive and fascinating field is surveyed in this volume and, second, by finding, often in unexpected places, valuable correlations or direct references to the neurologic sphere.

In regard to the first item, there are such interesting subjects as: discussion of the structure of heparin; the nature of hyaluronic acid and pathologic changes in synovial fluids; relationships between cell wall structure and bacterial capsular material; the structural framework of cartilage and connective tissues; the occurrence and possible significance of mucopolysaccharides in milk, in bacteria, in blood group substances, in epithelial mucus, in plasma proteins, and in urine; and the pharmacologic properties of certain polysaccharides in inflammatory reactions and in host resistance to bacterial and viral infections.

Items in the second category (those of more direct interest to neurology) tend to be scattered throughout the volume. A few examples are indicative of the profit which may be derived by detailed perusal: a brief discussion of polysaccharide abnormalities in gargoylism (pp. 12, 20-21); PAS staining characteristics and connective tissue structure (p. 116); glycoproteins of plasma (p. 245); gene interactions and blood group specificity (pp. 207-210); uridine nucleotides and polysaccharide synthesis (pp. 76-80); and pyretic action of bacterial lipopolysaccharides (p. 175).

The last two papers in the volume deserve special mention. Dr. Gottschalk of Australia has presented a very provocative study of the interaction between influenza viruses and the neuraminic acid of the host cell membrane, demonstrating that the virus uses the neuraminic acid moiety as an "anchorage" point to gain access to the host cell, but noting that the virus progeny raised within the cell are able to escape by means of a neuraminidase (or neuraminic acid destroying enzyme) so that they can subsequently invade other cells by the same anchorage mechanism. The relevance of these observations to neural tissues is obvious when it is recalled that the gangliosides of neurons contain neuraminic acid as an integral structural unit. Professor Klenk of Germany has presented a complementary study in the succeeding paper with a discussion of neuraminic acid itself, particularly its structure and relationship to gangliosides and similar compounds in mammalian cells.

This book is recommended to those who are interested in the advances of knowledge in a field likely to be unfamiliar to most of the neurologically trained but one which impinges in many ways upon neurology, including some relevant and important points of correlation.

D. B. T.

A Manual of Electrotherapy

A. L. Watkins. 1958. Philadelphia: Lea & Febiger. 259 pages. $5.00.

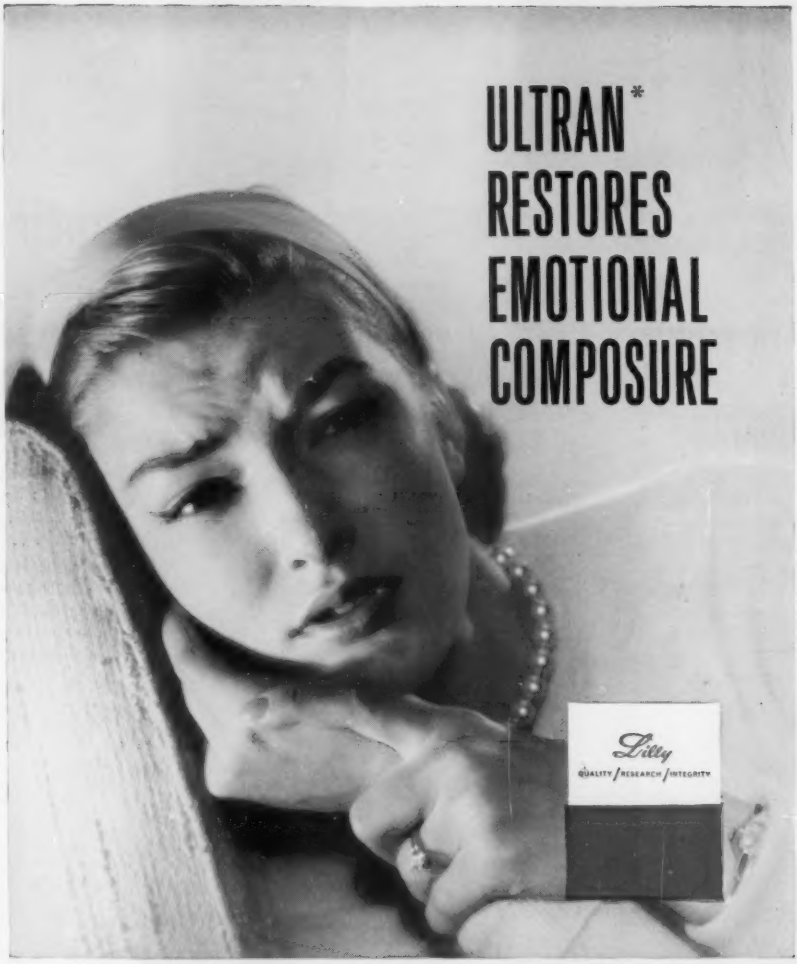
This extensively illustrated volume purports to show how, when, and where to use electrotherapy in the treatment of disease and injury. Based on the works of the late Richard Kovacs, it includes basic physics related to instrumentation and to treatment, an explanation of certain technics, and a new chapter on ultrasound. Electron microscopy is mentioned briefly, inadequately, and irrelevantly.

If this were an entirely new work instead of a revision and elaboration of a part of an old one, it would be easier to excuse frequent errors in spelling and punctuation, occasional lapses in physics and physiology, and the omission of a figure referred to in the text. We may presume that author and publisher wish *respiration* to be read for *perspiration* (page 22, last paragraph, line 5), *proton* for *protein* (page 85, paragraph 3, "The atoms of all the other elements are constituted by more than one protein and more than one electron."), one of the two figures 39 of pages 90 and 91 to be the figure 40 referred to in the text, and the Greek *sigma* to be substituted for the *alpha* four times on pages 152 and 153.

These and other careless lapses mar an otherwise clearly written book.

For us, the book has value less as a concise guide to which electrotherapeutic measures should be used in a variety of neurologic situations and more as a review of the physics underlying treatment and instrumentation.

J. L. O'L.



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This myelogram, made with the spot-film device, shows a herniated sixth cervical intervertebral disk. A concave filling defect of the *Pantopaque* column in the subarachnoid space is present, extending from the midportion of the body of the sixth cervical vertebra to the lower margin of the seventh cervical vertebra on the left side. The sheath of the nerve root between the sixth and seventh cervical vertebrae is obliterated, and the root sheath between the seventh cervical and first thoracic vertebrae is deformed. The cervical spinal cord is displaced slightly toward the right.

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

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Charles Van Buskirk, Treasurer

SEPTEMBER 1958

Merritt Now Acting Dean of Columbia Medical Faculty H. Houston Merritt, Director of the Neurology Service, has been appointed Acting Dean of the Faculty of Medicine of Columbia University and Acting Vice President in Charge of Medical Affairs. In addition to this new post, Dr. Merritt will continue as Columbia's professor of neurology and to direct the neurological service at the New York Neurological Institute. Since Merritt has been described as "one of a handful of men whose work led clinical neurology in the U. S. out of the blind alley of interminable classification and description of disease toward effective treatment" (Stethoscope, July-August 1958), the question has been raised as to how much his new appointment will interfere with his work for neurology. When queried on this point Merritt replied, "Not one iota, I shall just work harder, period!"

Harvey Cushing and EEG Societies Elect New Officers At its Twenty-sixth Annual Meeting at the Mayflower Hotel, Washington, D. C. (April 21-23), the Harvey Cushing Society elected Bronson S. Ray, President; David L. Reeves, Secretary; Hendrik J. Svien, Treasurer; Louise Eisenhardt, Historian; and Howard A. Brown, member of the Executive Committee.... The new officers of the American Electroencephalographic Society, elected at its annual meeting at Atlantic City (June 13), were: W. T. Liberson, President; Arthur A. Ward, Jr., President-Elect; Isadore Zfass, Treasurer; and Jerome K. Merlis, Secretary.

Cerebral Palsy Group Has Comprehensive Program A comprehensive program has been planned for the Twelfth Annual Meeting of the American Academy for Cerebral Palsy, to be held at the Sheraton Biltmore Hotel, Providence, R. I. (September 25-27). The program offers intensive instructional courses (September 24-27) on the diagnosis, treatment, and rehabilitation of the cerebral palsied plus a basic science course in the neuroanatomic and physiologic basis for cerebral palsy under the direction of Chester A. Swinyard. The tentative program for the general scientific sessions includes a presidential address by William T. Green; obstetrical factors in the etiology of cerebral palsy (Nicholson J. Eastman); spontaneous intracranial hemorrhage in childhood (Donald Matson); vascular abnormalities versus local tissue abnormalities in cerebral palsy (Orville Bailey); role of

paranatal venous thrombosis in the causation of cerebral palsy (Cyril B. Courville); prenatal effects of experimental radiation exposure (Samuel P. Hicks); and many other provocative basic science and clinical presentations. The instructional courses and general scientific questions will be supplemented by question-and-answer periods during luncheon sessions and by special audiovisual sessions.... The social program comprises a cocktail party followed by a banquet and dancing (September 25); a clambake (September 26), preceded in the afternoon by a tour of the Rhode Island School of Design and the Museum of Art; and an open house reception by Eric Denhoff and his staff at the Meeting Street School.... Registration for members is free, for nonmembers $15. There is an "all-inclusive plan" for registration which includes the instructional courses, the general sessions and all social events of $35 for members, and $50 for nonmembers. Chairman of Committee on Local Arrangements is Eric Denhoff, 293 Governor Street, Providence 6.

Laboratory of Neurochemistry To Be Established at Stanford

A new Stanford Medical School laboratory, the Koshland Laboratory of Neurochemistry, will be established with the aid of funds for basic equipment from Daniel E. Koshland, president of Levi Strauss & Co., San Francisco. Aid for the conduct of the research program during its first three years is supplied by a grant from the National Institute of Neurological Diseases and Blindness. The head of the new laboratory is AAN member, Elizabeth Roboz, associate professor in neurology and medical microbiology.

NNRF Announces First Awards

The Scientific Committee* of the National Neurological Research Foundation announces that three neurologic scientists will receive research fellowship awards of $10,000 to $12,000 a year for five years. The three selected are: Michael V. L. Bennett, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York City; Byron H. Waksman, Harvard University School of Medicine, Boston; Dixon M. Woodbury, Department of Pharmacology, University of Utah College of Medicine, Salt Lake City. Further information or application forms for these awards may be obtained from Mrs. Rodgers Denckla, the National Neurological Research Foundation, 3255 N Street N. W., Washington 7, D. C.

Conference on Research and Training in Mental Retardation

A conference on research and training in mental retardation is to be held at Virginia's Lynchburg Training School and Hospital in Colony, under the direction of Benedict Nagler, the new superintendent (September 11-12). The participants are out-

*Raymond D. Adams, Edward M. Dempsey, Louis S. Goodman, Seymour S. Kety, Oliver Lowry, Horace W. Magoun, James L. O'Leary, and A. Earl Walker.

standing leaders in neurology, psychiatry, psychology, education, social work, and nursing. A highlight of the program is a symposium on neurological research in mental retardation under the chairmanship of Richard L. Masland. Also participating in this program are Francis M. Forster, Clemens E. Benda, and Paul I. Yakovlev.

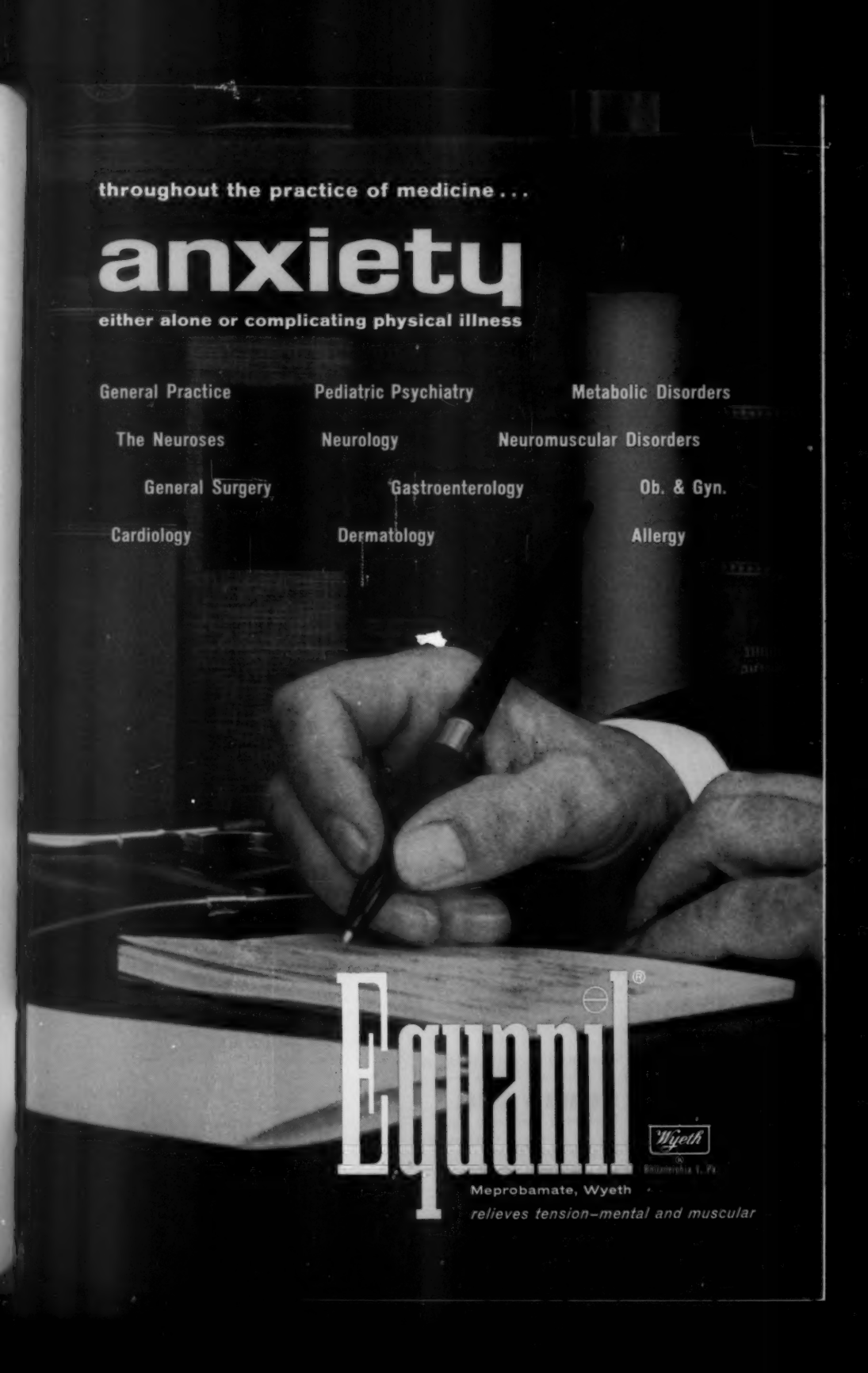
Psychopharmacologists To Convene in Spain The Section of Psychopharmacology of the Fourth International Congress of Psychotherapy will meet in Barcelona, Spain (September 1-7). Its program will emphasize the practical, scientific, and nonspeculative aspects of the biochemistry, pharmacology, and therapy of normal and abnormal mental activities. The official languages are English, French, German, and Spanish. Additional information and inscription blanks may be obtained from: Catedra de Farmacologia, Facultad de Medicina, c. Casanova, 143, Barcelona.

New Committee Formed To Study Industrial Neurology For years the Council on Industrial Health of the American Medical Association has received requests from industrial physicians for advice on the employment of persons affected by neurological disorders. As a response to this growing need for a study of neurological conditions in industry, the AMA has established a Committee on Neurological Disorders in Industry to operate under its Committee on Scientific Development of the Council of Industrial Health. Heading this newly formed committee is Melvin D. Yahr, and serving with him are Benjamin Boshes, Francis M. Forster, Harry Sands, Pearce Bailey, Robert Garber, and Augustus Rose.... The committee, among whose many objectives is development of better communications between industrial physicians and neurologists, held an organizational meeting at the Claridge Hotel, Atlantic City (June 15).

Briefs A. B. Baker was elected to the American Board of Psychiatry and Neurology from the Section of Nervous and Mental Diseases of the AMA.... H. Houston Merritt has been appointed to the Special Medical Advisory Group of the VA to represent neurology.... Professor A. Bairati, Director of the Anatomical Institute of the University of Milan, Italy, has just completed a six months' assignment as a Visiting Scientist to William F. Windle's branch in neuroanatomical sciences of the NINDB; Professor Bairati was collaborating with Sanford Palay in studies on electromicroscopy.... A recent lecturer (July 9) at NINDB was Professor Ujihiro Murakami of Nagoya University, Japan; his topic was the pathogenesis of congenital malformations of the central nervous system.... Three new members of the NINDB National Advisory Council will assume their duties as Council members in September; they are Dr. Jacob Yerushalmy, Professor of Biostatistics, School of Public Health, University of California; Dr.

Francis M. Forster, Professor and Director, Department of Neurology, Georgetown University School of Medicine; and Dr. Clinton N. Woolsey, Department of Physiology, University of Wisconsin.... Arthur S. Fleming, former President of Ohio Wesleyan University, is the new Secretary of Health, Education, and Welfare, succeeding Marion B. Folsom, who resigned for reasons of health.... The next examinations of the American Board of Psychiatry and Neurology will be December 15-16, 1958, in New York and March 16-17, 1959, in New Orleans; all communications should be addressed to Dr. David A. Boyd, Jr., Secretary-Treasurer, Mayo Clinic, Rochester, Minn.... The Sixty-ninth Annual Meeting of the Associated Medical Colleges will be held at the Sheraton Hotel, Philadelphia, on October 13-15.... The new offices of the United Cerebral Palsy are 321 West 44th Street, New York City.... Recently the address of the Executive Offices of the American Academy of Neurology, Mrs. J. C. McKinley, Executive Secretary, has been changed from 3501 East 54th Street to 4307 East 50th Street, Minneapolis 17, Minn.; the new telephone number is PArkway 4-4409.

Pearl Bailey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For relatively mild essential hypertension, 2 Filmtabs are given initially, with 1 or 2 Filmtabs daily as maintenance. For anxiety, tension, and nervousness, the range may vary from 1 to 4 Filmtabs.

FELLOWSHIPS for training in NEUROCHEMISTRY

A postdoctoral training program in NEUROCHEMISTRY is being organized with the financial support of the National Institute of Neurological Diseases and Blindness, U. S. Public Health Service, under the auspices of the Dept. of Biochemistry and of Neurology, College of Physicians and Surgeons, Columbia University. It will provide general training in advanced theory and methods of biochemistry and physical chemistry; courses and seminars will be given by outstanding investigators. The special aim of the program, in addition to giving a broader background in general biochemistry, is to make the trainee familiar with current problems in neurochemistry and to offer guidance to research in this field.

There are several fellowships available for periods of 2 to 3 years. This stipend is dependent on previous experience. A doctor's degree in chemistry, biology or medicine is prerequisite. For application or information write to:

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Meprobamate brought symptomatic relief to 105 of 145 psychiatric patients "representative of the entire hospital population," 70 of whom obtained pronounced to moderate relief.*[1]

1. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Emotional disorders treated with meprobamate and promazine. Connecticut M. J. 21:1047, Dec. 1957.

SYMPTOMATIC IMPROVEMENT

(hospitalized patients—all types)

by disease

DIAGNOSIS	NO. OF PATIENTS	NO. IMPROVED
SCHIZOPHRENIA		
PARANOID	7	2
NON-PARANOID	45	34
DEPRESSION		
PSYCHOTIC†	37	25
NEUROTIC	16	10
ANXIETY STATE	9	8
CHARACTER DISORDERS	15	13
OTHERS	16	13
TOTALS	145	105

by symptom

SYMPTOM	NO. IMPROVED
SLEEP DISTURBANCES	36
ANXIETY	30
TENSION	31
AGITATION	8
OTHERS	11
TOTAL	116

†Relief mainly in symptoms of anxiety, tension and insomnia.

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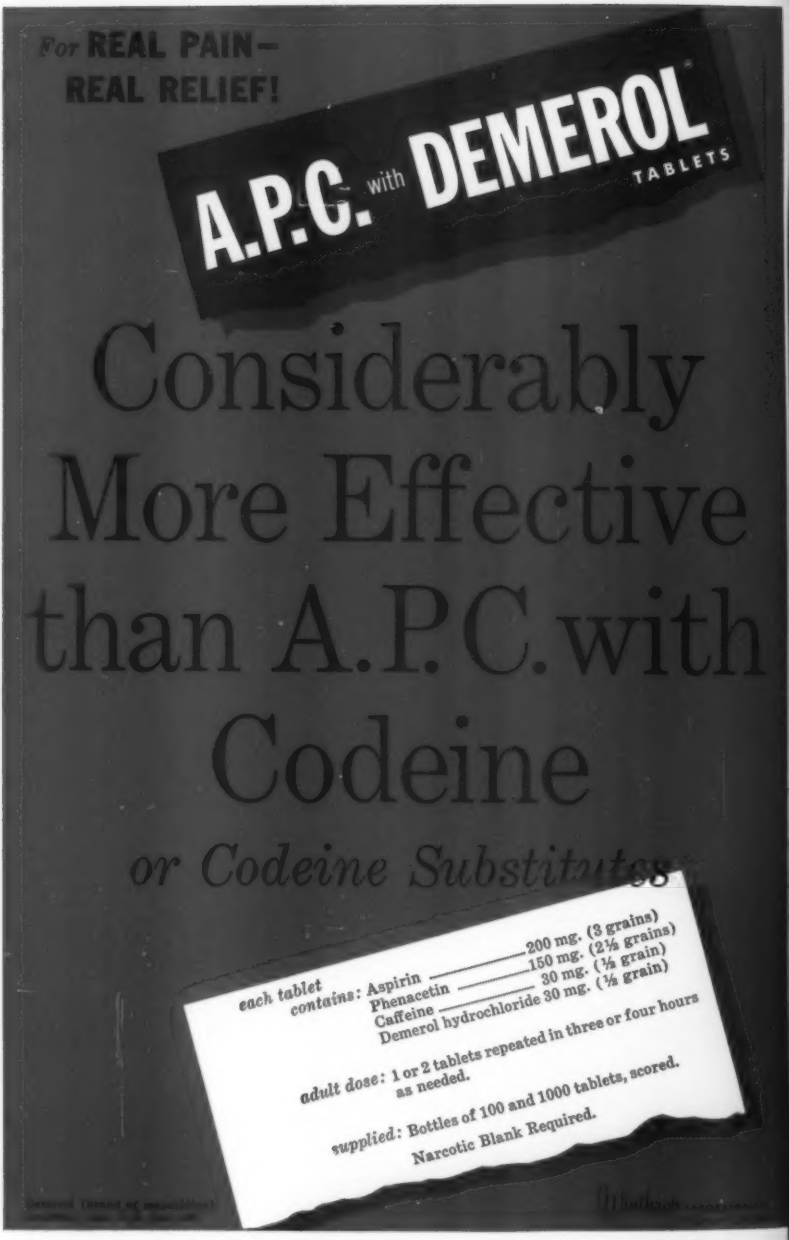
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